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Structure of Cytochrome-Containing Photosynthetic Reaction Centers From Chromatium minutissimum in Solution and in Langmuir-Blodgett Films

917C0319 Moscow BIOLOGICHESKIYE MEMBRANY in Russian Vol 7 No 11, Nov 90 (manuscript received 13 Jun 90) pp 1138-1143

[Article by R. L. Kayushina, V. V. Yerokhin, A. T. Dembo, Ya. Sabo, P. P. Noks, and A. A. Kononenko, Institute of Crystallography imeni A. V. Shubnikov, USSR Academy of Sciences, Moscow; Biology Department, Moscow State University imeni M. V. Lomonosov]

UDC 539.216.2:577.112

[Abstract] Owing to the fact that x-ray structural analysis has been used to provide a detailed description of the structural features of the reaction center/cytochrome complex in crystalline state for only one of many varieties of bacteria, the researchers chose to examine a similar complex (multiheme cytochrome c + photosynthetic reaction center) from the membranes of the chromatophores of the purple bacteria *Chromatium minutissimm.* Small-angle x-ray scattering revealed a whole-particle gyration radius R_g of 35.5 + 1 angstroms. L_{max} was found to be 110 + 10 angstroms. The symmetrical positioning of the main maximum *p(r)* relative to the L_{max} indicates that the particle is nearly spherical. The period of the Langmuir superlattice was d = 115 + 1 angstroms. Figures 3; references 14: 7 Russian, 7 Western.

Structural Changes in Conducting Langmuir-Blodgett Films of a Mixture of Hexadecyl-TCNQ and Hexadecyl-BEDT-TTF

917C0319B Moscow BIOLOGICHESKIYE MEMBRANY in Russian Vol 7 No 11, Nov 90 (manuscript received 23 Apr 90) pp 1165-1172

[Article by T. S. Berzina, V. I. Troitskiy, and L. G. Yanusova, Scientific Research Institute of Physical Problems imeni F. V. Lukin, Moscow; Institute of Crystallography imeni A. V. Shubnikov, USSR Academy of Sciences, Moscow]

UDC 539.216.23

[Abstract] In the production of Langmuir-Blodgett films for nanotechnology, stability of conductivity over time is critical. In earlier work, the researchers here by-passed doping to produce conduction films of donor molecules of hexadecyl-BEDT-TTF and acceptor molecules of hexadecyl-TCNQ. Subsequently, they found that when samples were immersed in hexane, the applied film remained completely intact. Afterwards, they also found that the film exhibited better morphology and conductivity than did the initial film and that it kept its properties for at least three months. In the work reported here, the researchers sought to determine the reasons for those phenomena by studying hexadecyl-BEDT-TTF/hexadecyl-TCNQ films before and after hexane treatment. Electron microscopy, electron diffraction, and small-angle x-ray scattering studies indicated that such films form two-phase systems. One phase is sparingly soluble in hexane. After samples coated with the films were treated in the hexane, that phase remains on the substrate and, as a result of recrystallization, produces a uniform conducting film with stable properties. Electronography and x-ray structural analysis revealed that application of the film apparently results not in layering into phases of individual components or deposition of single-component impurities in the film, but in the formation of two complexes with charge transfer of differing composition between the donor and acceptor molecules. Figures 4; references 12: Western.

Isomerization of 1-(*p*-Chlorophenyl)-2-(α-Naphthyl)ethylene in Solution, Photosensitized With a Ruthenium Complex Langmuir Film

917C0319C Moscow BIOLOGICHESKIYE MEMBRANY in Russian Vol 7 No 11, Nov 90 (manuscript received 15 May 90) pp 1173-1176

[Article by D. A. Styrkas, I. K. Lednev, and M. V. Alfimov, Branch of Institute of Chemical Physics, USSR Academy of Sciences, Chernogolovka, Moscow Oblast]

UDC 539.216.2

[Abstract] In studying the efficiency of the photocatalytic properties of $Ru(C_{17})_2^{2+}$-based Langmuir-Blodgett multilayers, the researchers here investigated Langmuir-Blodgett-photosensitized *trans-cis*-isomerization of 1-(*p*-chlorophenyl)-2-(α-naphthyl)ethylene in solution and the extinction of the $Ru(C_{17})_2^{2+}$-based film with a hydrophilic extinction solution. The isomerization kinetics were defined by the equation $\ln[(A-A_s)/(A_0-A_s)] = -at$, where A_0, A, and A_s represent the optical absorption of the solution at the initial moment in time, at the present moment in time, and with stationary illumination; t is photolysis time; $a = k_q\tau_0 k_1[Ru^{2+}]$; and τ_0 is lifetime of the luminescence of the ruthenium complex. The researchers found a linear dependence between growth in a and growth in the number of monolayers in the Ruthenium-based Langmuir-Blodgett film, which points to the additive contribution of the surface and deep layers during the sensitized isomerization. That may be due to the swelling of the film during incubation in solution or to the efficient migration of energy within the film and to its surface reaction. Luminescence extinction was studied with an aqueous solution of $CuSO_4$, which, as it turned out, did not penetrate deep into the film. There was, however, a mild suppression of luminescence, which indicates the absence of efficient energy transfer to the film surface. Figures 4; references 6: Western.

Determination of the Structure of Stilbazole Salt Langmuir-Blodgett Films With Fourier IR Spectroscopy

917C0319D Moscow BIOLOGICHESKIYE MEMBRANY in Russian Vol 7 No 11, Nov 90 (manuscript received 15 May 90) pp 1177-1181

[Article by A. V. Sukhorukov and D. A. Styrkas, Institute of Spectroscopy, USSR Academy of Sciences, Troitsk, Moscow Oblast; Branch of Institute of Chemical Physics, USSR Academy of Sciences, Chernogolovka, Moscow Oblast]

UDC 539.216.2

[Abstract] One of the most widely studied classes of compounds that enable the formation of Langmuir-Blodgett multilayers is substituted stilbenes, which are used as probing elements to determine the orientation of molecules around the probe, as elements for nonlinear optical converters, and, among other things, as modeling compounds in the study of sensitized isomerization. In light of that, studies of the planar structure of Langmuir-Blodgett multilayers formed with substituted stilbenes take on great significance. The researchers in the work reported here used Fourier IR spectroscopy to determine the arrangement of hydrocarbon tails in Langmuir-Blodgett multilayers formed with stilbazole salt in relation to a hard silicon substrate. They found that the films had no preferred axes of orientation of hydrocarbon chains of molecules in the plane of the samples studied. The angle of inclination of the hydrocarbon tails of the salt molecules was 54 + 4° in relation to the sample plane. Figures 3; references 13: Western.

Pyro- and Piezoelectric Activity of Multilayer Langmuir-Blodgett Films Based on Azocompounds

917C0319E Moscow BIOLOGICHESKIYE MEMBRANY in Russian Vol 7 No 11, Nov 90 (manuscript received 24 May 90) pp 1182-1186

[Article by P. N. Davydova, V. V. Lazarev, V. A. Khavrichev, and S. G. Yudin, Scientific Research Institute of Organic Semifinished Products and Dyes, Moscow]

UDC 539.216.2

[Abstract] The pyroelectric and piezoelectric figures of merit (γ/ε and d_{33}/ε, respectively) for the best materials used in electronic instruments are approximately (0.5 - 1.0) x 10^{-9} C/cm2/K and (1 - 2) x 10^{-12} C/N. Although the values achieved thus far for polar Langmuir films are almost an order of magnitude lower, it is possible to use Langmuir technology to produce ultrasensitive elements that are much thinner than single-crystal and ceramic materials—a fact that makes the use of pyroelectric and piezoelectric Langmuir-Blodgett films attractive in microelectronics. That prompted the researchers here to study the pyroelectric and piezoelectric activity of azo-compound-based (*X*-type) films consisting of approximately 100 layers and produced with the Langmuir-Schaefer method at a surface pressure corresponding to the liquid-crystal state of a monolayer on a water surface. The samples that were investigated had a sandwich structure on a glass substrate, with the monolayers placed between two sprayed aluminum electrodes. The researchers found that the figures of merit dropped with decreasing length of the hydrocarbon chain. For short-chain homologs, the sign of the figures of merit reversed. Both the pyroelectric and piezoelectric signals displayed a linear dependence on the external constant electric voltage. The researchers found the γ/ε for the films to be 5 - 50 pC/cm^2/K and the d_{33}/ε, 0.3 - 2 pC/N. Figures 3; references 4: 3 Russian, 1 Western.

Interrelationship of Optical and Morphological Properties of Langmuir-Blodgett Films of Phthalocyanins of Copper and Vanadium

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[Article by I. V. Gavrilyuk, Z. I. Kazantseva, P. V. Lavrik, A. V. Navok, B. A. Nesterenko, Yu. M. Shirshov, and V. I. Stepkin, Institute of Semiconductors, UkSSR Academy of Sciences, Kiev]

UDC 539.216.2

[Abstract] The fact that phthalocyanin Langmuir films are among the most promising for use in molecular electronics in terms of the creation of layered structures with alternating conducting and dielectric regions and the fact that earlier research demonstrated a link between physical properties and structure prompted the researchers here to investigate the correlation between structure and optical and electrical properties in films of tetrasubstituted vanadyl phthalocyanin $4R_1$-VOPc (R_1 = SO_2-NH-$C_{18}H_{37}$) and copper phthalocyanin $4R_2$-CuPc($R2$ = $C(CH_3)_3$). Substrates were gold on glass, silicon, and oxidized silicon. Elipsometry and optical and scanning electron microscopy revealed an anisotropy for the physical properties of both films that was due to the shapes of the molecules themselves and to the two-dimensional crystal structure of the films caused by the presence of oriented substrate defects, which suggests that the properties of the films can be controlled by modifying the substrates. Figures 7; references 7: 1 Russian, 6 Western.

Adsorption of Ammonia Vapors by Langmuir Films of Crown Ethers

917C0319G Moscow BIOLOGICHESKIYE MEMBRANY in Russian Vol 7 No 11, Nov 90 (manuscript received 17 Apr 90) pp 1205-1209

[Article by S. M. Balashov, V. V. Kislov, V. V. Lapachev, I. E. Nevernov, A. Yu. Potapov, and G. B. Khomutov,

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UDC 538.975

[Abstract] Researchers have devoted a great deal of attention to Langmuir-Blodgett films in the last 10 years because of their ability to adsorb various substances. The high degree of uniformity and order of such films makes them excellent active elements for various types of sensors. The work reported here approached a study of crown ethers with hydrophobic hydrocarbon tails from the standpoint of their use in Langmuir-Blodgett technology to create chemical sensors. The researchers chose to examine the ability of the ethers to adsorb NH_3 because the tetrahedral arrangement of charge at NH_3 optimizes the topology of its interaction crown compounds. Crown CO-21, crown 22, and 18-crown-6 were used in the study. The π-A isotherms of the crown ethers (particularly CO-21) indicated their suitability for use in Langmuir-Blodgett technology. The researchers suggest that, although the adsorption qualities of the ethers remain open to question, they can be used for detection of HN_3 vapors in the atmosphere. Transfer of the films to substrates of oxidized silicon and quartz glass showed that CO-21 transfers best, probably because of the C = O bond. Figures 3; references 9: 3 Russian, 6 Western.

Industrial Microbiology and Biotechnology in Latvia

917C0426A Riga IZVESTIYA LATVIYSKOY AKADEMII NAUK in English No 12, Dec 90 pp 65-76 (manuscript received 29 Aug 90)

[Article by M. Beker, Latvian Academy of Sciences, Institute of Microbiology]

[Text] In the last century Riga and the whole of Latvian territory witnessed a rapid development of the fermentation industry to which the initiation of biotechnological production is referred. Before World War II there were 64 distilleries in Latvia: in Riga there were localized breweries, modern for that time, baker's yeast production, fruit-and-berry wine productions. Such plants as "Volfschmidt", "Kimmel", "Tanheizer", and later "Aldaris" were widely known. Latvian dairymen could produce the most popular European cheeses. In the 1930's, the "Kleisti" serum station started producing veterinary and medical immunopreparations.

In the 1950's, citric acid and antibiotic production rapidly increased. In the 1960's, a bacterial nitrogen fixing "Nitrogin" was developed and introduced into practice, animal feed antibiotic, amilolytic enzyme, animal feed vitamin B_{12} and lysine feed concentrate, as well as fodder yeast productions were initiated. Itaconic acid production was developed and organized. From the 1970's through today, one of the central parts in the Republican biotechnological programmes was occupied by bioconversion: technology and equipment have been worked out for waste methane fermentation and animal fed proteinization. Worth mentioning are works on "Mikrocit" and "Fuzikokcin" production, as well as on obtaining a preparation for plant growth stimulation, starter culture "Lacterin" for fodder silaging, biological agents of plant protection.

Industrial microbiology in the 1980's is associated also with the development of the medical enzyme L-asparaginase and ribonuclease and with the production of biopolymers β-polyoxybutyrate and levan.

If before 1940 microbiological and biotechnological industries developed on the basis of private initiative and free market laws, the Soviet power having been established there started a "planned" economy. In reality the development of the industry and science was dictated by party resolutions and individual administrative persons who solved urgent problems by campaigns. Based on the experience in liquidating small and organizing huge enterprises in the USSR, it was mechanically done here also. An example—closing of distilleries.

Highly skilled specialists and workers was one of the reasons why comparatively big experimental productions of new products (antibiotics, biochemical reagents, lysine, citric acid, etc.) which were to solve all-union problems were organized in Latvia. Organization of big enterprises aggravated the ecological situation, supply of raw materials and energy, caused disastrous social problems due to labor power immigration from other regions. A stagnation in general technical development has led to a situation when science became prevalent to industry which lost material incentives and was not capable of instilling scientific outputs into production. Hence, today, Latvia has a great potential for the biotechnological science with limited local application possibilities. A way out would be privatization of production and a wide international cooperation.

Research Centres and Subjects of Work

Before the war there were no special centres of technical microbiology and biotechnology in Latvia. At fermentation enterprises in Riga there worked high class foremen who were consulted mainly by foreign scientists. The University, beside training work, was doing very specialized investigations. However, we have to mention here Professor Delle's wine stability grade which he discovered in the beginning of this century, and the world is using Delle units. Significant is Professor Kirchenstein's dairy microbiology and works on developing immunopreparations done together with Professor Darzins. Worth mentioning is also K. Kreslins who, when working in Leningrad, attained skill in obtaining malein. Professor A. Kalnins should not be forgotten with his works on pentinase-containing preparation for flax processing and nitrogen-fixing microorganisms which were later on used to work out bacteriological fertilizers. Microbiological investigations on various institutions in Latvia are seen in Table 1.

Table 1. Industrial Microbiology and Biotechnology in Latvia

Institution	Field of investigation	Leading research workers
Institute of Microbiology, Latv. Acad. Sci. and its Experimental Plant	Biosynthesis of biologically active substances (amino and organic acids, enzymes, hormones, polysaccharides); bioconversion of organic substances and waste treatment. Obtaining of producers; their physiology and biochemistry. Gene engineering. Transgenic plants. Cell anabiosis; regulation of metabolism; bioenergetics; cell ultrastructure; cell and enzyme immobilization; immunovirology, embriotransplantation, fermentation and down-stream processing	Problem supervisors: Prof. Acad. R. Kukaine, Prof. Acad. M. Beker. Theme supervisors: Prof. Acad. U. Viesturs, Prof. Acad. R. Karklins; Dr Sci. (Biol.) J. Shvinka; Cand. Sci. (Biol.): R. Ozolina, J. Jakobsons, I. Miske, E. Miklasevics, V. Luka, I. Vina, D. Zarina, V. Loza, J. Meldrajs, U. Banders, S. Laganovskis, V. Berzins; Dr Sci. (Med.): A. Muceniece, A. Ferdats, L. Nagayeva, S. Chapenko; Cand. Sci. (Med.): G. Feldmane, M. Kalnberza; Cand. Sci. (Tech.): R. Are, A. Upitis
Institute of Organic Chemistry, Latv. Acad. Sci. and its Experimental Plant	Molecular biological studies of microorganisms. Gene engineering. Biosynthesis and modification of antibiotics	Prof. Acad. E. Grens; Cand. Sci. (Biol.): P. Pumpens, V. Berzins, V. Kleiners; Cand. Sci. (Chem.) A. Veinbergs

Table 1. Industrial Microbiology and Biotechnology in Latvia (Continued)

Institution	Field of investigation	Leading research workers
Institute of Biology, Latv. Acad. Sci	Development of biological preparations for plant protection. Biotechnology of embryocultures of plants	Cand. Sci. (Biol.): J. Zarins, J. Rasels
Institute of Wood Chemistry, Latv. Acad. Sci.	Bioconversion of lignocellulose substrates	Prof. Acad. U. Viesturs; Cand. Sci. (Biol.) J. Katkevichs
Latvian University and its Botanical Garden, as well as Botanical Garden Latv. Acad. Sci.	Conversion of nucleic acid base. Gene engineering of microorganisms. Meristem technology of decorative plants	Prof. H. Maurina; Cand. Sci. (Biol.) I. Muiznieks; Prof. R. Kondratovich; Cand. Sci. (Biol.) K. Buivids
Riga Technical University	Isolation and investigation of products of microbial synthesis	Prof. Acad. E. Gudriniece
Latvian Academy of Agriculture	Treatment of dairy industry by-products. Microbiology of nitrogen fixing bacteria. Plant viruses and preparations for plant protection. Meristem technology of fruit trees	Prof. P. Zarins; Prof. V. Klasens; Prof. V. Prieditis; Prof. I. Gronskis
Association "Biolar" Institute of Applied Biochemistry	Obtaining of biochemical reagents by microbiological methods	Prof. U. Mikstais; Dr A. Pavars; Cand. Sci. (Chem.): A. Arens, O. Stengrevics; Cand. Sci. (Techn.) Z. Viesture

In 1946 the Latvian Academy of Sciences was founded, including the Institute of Microbiology on the bases of the serum station "Kleisti". Yet the production of biological preparations such as vaccines of porcine measles serum, bovine tuberculine, scarlatine serum, smallpox vaccine, diphtheria anaboxine, antiviral and antituberculosis vaccines, and insulin was interrupted as this production was monopolized by the USSR. The Institute of Microbiology is today a principal research centre of industrial microbiology and classical biotechnology in Latvia. There are more than 500 people working, 65 percent of them are employed in the field of microbiology and biotechnology. The number of doctors of science at the Institute—11, candidates—91. Seven research laboratories mainly deal with microbiological biosynthesis and bioconversion of biologically active substances (see Table 1). Both fundamental and applied aspects of the problems have been scrutinized. When choosing an investigation object one has to take into consideration a novelty of possible results, a probability of instilling those results into practice, especially for the needs of the Republic. The staff of the Institute is capable of solving all the stages of a biotechnological complex: search for a producer in nature, the selection of it by classical and gene engineering procedures, a detailed physiological, biochemical and ultrastructural investigation of prospective producers, an optimization of nutrient media and the fermentation process, as well as the development of substance isolation and purification. As the Institute has pilot installations and an Experimental Plant (Biochemical Preparation Plant), any technological process can be installed. It is even possible to modernize fermentation installations according to special bioengineering designs. Biotechnological processes developed for agricultural needs are optimized in production conditions at two basic laboratories which localize at the agricultural firm "Uzvara" and the "Ogre" farm. Most significant biotechnological processes and preparations developed at the Institute are shown in Table 2.

Table 2. Biotechnological Developments of the Institute of Microbiology and Its Experimental Plant

Item	Description of process production	Stage of the development and investigation
Lysine food concentrate	Many high yielding procedures selected. A semicontinuous fermentation procedure worked out and an original wasteless technology of producing liquid and dried lysine concentrate developed	Instilled in 5 plants in the USSR, which produce about 30,000 t lysine a year. Licenced
Lysine concentrate application in plant-growing	A method worked out of seed pest control and stimulation of plant growth, as well as plant microflora	Developed recommendations in cooperation with Rostov-on-Don University for applying the preparation and data of efficacy drawn up
Vitamin-amino acid premixes on the basis of lysine concentrate	A technology and various compositions worked out of enriching feed of various domestic animals with vitamins and amino acids	Production mastered at the Livani Biochemical Plant. Data on efficacy drawn up
Citric acid	Productive strains selected and a technology of intensive surface fermentation in molasses nutrient media, as well as a technology for submerged fermentation for processing paraffins worked out. Wasteless technological processes have been mastered for the production of food, technical and reagent pure citric acid. A technology of obtaining a starter culture instilled	Experimental production in Riga. The technology used in the USSR and other foreign countries

Table 2. Biotechnological Developments of the Institute of Microbiology and Its Experimental Plant (Continued)

Item	Description of process production	Stage of the development and investigation
Itaconic acid	Productive strains selected and a technology of obtaining the starter culture-seed material, as well as a process of producing itaconic acid in the molasses nutrient medium worked out	Production instilled in Latvia and 2 plants in the USSR
Nitragin	Local strains isolated for alfalfa, clover, peas, lupin. Their surface and submerged fermentations, as well as dehydration with the contact-convective procedure instilled and mastered	Instructions for an experimental production prepared
Epiphytic plant stimulators	Two active bacterial cultures isolated which stimulate vegetable and cereal seed shooting, as well as their rooting and growth intensity	Experimental production started and application procedures worked out
Plant stimulator "Mikrocit"	A bacterial culture has been isolated which accumulates phytohormones in the fermentation medium	Experimental production started and application procedures worked out
Sucrose bioconversion for obtaining levan, fructose, sorbitol	Producers selected and an experimental technological process worked out	Experimental samples obtained in a pilot installation and a wide study of the levan application in medicine and food industry done
Poly-β-oxybutyrate	A producer selected and an experimental technological process worked out	Samples obtained and an investigation into the application of the product done
Interferon inducer "Lariphan"	The fermentation and isolation mastered, as well as some preparative forms developed	Experimental production and clinical trials undertaken
L-asparaginase	An original producer selected and a technological process for the production of the immobilized enzyme developed	Experimental samples obtained and medical trials performed
Ribonuclease	The production of an immobilized enzyme preparation worked out	Experimental samples obtained and medical trials performed
Yeast lipase	The production and experimental technical enzymatic preparation worked out	Production of small batches and application in fell processing
Feed biological preservers (starter culture)—"Laktorin" and semi-solid products	Producers selected and a technology of producing and using worked out	Production and application of the liquid preserver mastered; a dry preparation is under development
Fuzikokcin	The microbiological synthesis and the isolation of the preparation from the culture liquid mastered	Developed in cooperation with the Institute of Agricultural Biotechnology of the USSR Academy of Agricultural Sciences. Experimental production initiated
Proteinization of the starch-containing fodder	A producer selected and production mastered	Used at the agrofirm "Uzvara"
Fractionation of herbage (TPF-1 process)	The production of liquid protein products from alfalfa, clover, grass mixture, sugar-beet leaves employing biotechnological processing of liquid and solid fraction mastered	Used at the agrofirm "Uzvara"
A technology of methane fermentation of domestic animal waste and food industry waste waters	The treatment of pig slurry, bird dung, plant brown juice, milk processing, yeast, starch and sugar industry waste waters mastered obtaining biogas and a harmless liquid fraction	Technological instructions prepared, as well as shop drawings, the description of bioreactors and the production experience at numerous enterprises
Isocitric acid and its salts	A producer selected and a technology for fermentation, isolation and purification developed	Produced at the MBI Experimental Plant of Biochemical Preparations
Gluconic acid	Producers selected and a technology of the crystalline product production developed	Production mastered at the MBI Experimental Plant of Biochemical Preparations
Gluconic acid and borate anticorrosion preparation	A technology of the production and application of the preparation worked out	Developed in cooperation with the Institute of Inorganic Chemistry, Latv. Acad. Sci. Production mastered at the MBI Experimental Plant of Biochemical Preparations
Active dried baker's yeast	A culture resistant to dehydration and a technology using potato juice as a nutrient medium developed	Experimental samples obtained
Active cultures of dried wine yeast	A culture collection selected and a technology for preparation and dehydration worked out	Experimental samples obtained
Acidophyllic milk "Narine"	The culture supplied by the Institute of Microbiology of the Armenian Acad. Sci. adapter for the dairy industry of the Latvian Republic	Production of the culture at the Republican Children's Hospital and at the MBI to order

Table 2. Biotechnological Developments of the Institute of Microbiology and Its Experimental Plant (Continued)

Item	Description of process production	Stage of the development and investigation
Trichodermin	A producer selected and a technology developed for the production of the liquid preparation for biological protection against plant diseases	Experimental samples obtained and tests conducted
Azotobacterin	A producer selected and a technology of the production of the liquid preparation developed	Samples selected and tests conducted
Immobilized yeast with an invertase activity	A yeast culture obtained with high invertase activity; a technology worked out of the biomass production and cell immobilization, as well as a technology of sucrose inversion	Developed in cooperation with Tallinn Polytechnical Institute. Samples obtained and a pilot installation designed
Luteinized hormone preparation	A technology worked out of isolating the hormone from the pig hypophysis, as well as methods of the application, of the preparation, also for cattle embrya transplantation	Experimental batches obtained at the OSI Experimental Plant and tests on cows
Bovine antileukemic system	Methods of diagnosing leukemia in infected animals and a vaccine worked out	Production of experimental diagnostic kits and the vaccine started
Immunomodulator on the basis of enteroviruses	A biopreparation developed for the therapy of various malignant tumors	Preparation obtained at the MBI to order, and wide clinical trials performed
Diagnostic kits of hepatitis A and B	Immunoenzymatic tests employing the monoclonal antibody technique worked out	Experimental samples obtained
Diagnostic kit for plant viroid diseases	With the help of the molecular hybridization procedure, a diagnostic kit for diagnosing potato and chrysanthemum viral diseases obtained	Experimental test kits obtained and tested on infected plants
Extract of ginseng cells	Cell surface culture obtained and the technology of the extract production and application worked out	Experimental batches obtained and tested in food industry

There are more Institutes of the Latvian Academy of Sciences which are working on biotechnological problems, for instance, the Institute of Organic Synthesis where they are solving mostly molecular-biological aspects and gene engineering problems. At the Institute of Wood Chemistry a technology of feed yeast production on the basis of wood and peat hydrolysis was developed; specialists of this Institute are working also at enzymatic and microbiological bioconversion of lignocellulose substrates.

The Institute of Biology is working on biological preparations for plant protection. The Botanical Garden employs meristem cultures for flower recovery, in selection and multiplication.

The association "Biolar" Institute of Applied Biochemistry at Olaine has developed into an important centre of industrial microbiology and biotechnology. This Institute employs about 400 people, including four doctors of science and 60 candidates. Most of the specialists are chemists who research in originating new biochemical reagents. During twenty years about 2,000 compounds were selected, the reagent production and analysis procedures were developed in close cooperation with the USSR Academy of Sciences, Republican, especially Latvian Academy of Sciences, Institutes and various Research Centres. An important predecessor of many antibiotics is alpha-aminophenylacetic acid, and a technology of its production has been worked out by the "Biolar" specialists. Most important "Biolar" products are shown in Table 3.

Table 3. The Contribution and Perspectives of the Association "Biolar" Institute of Applied Biochemistry

Item	Examples	Notes
Enzymes	Tripsin, Pepsin, Phosphatases, Carboxypeptidases, Lysocime, Peroxydase, Catalase, Urease, Endonucleases, Nucleases, Lucipherses	Mostly for research needs. There are 100 items total, 30-40 of which are produced regularly each year
Reagents in immunochemistry	Immunoglobulins and their conjugates with enzymes for diagnosing plant viral diseases. A reagent kit for detecting peroxydase label with the help of hemiluminiscences	Mostly in cooperation with the Production Association "Meristemic Cultures" at Ogre
	A reagent kit for detecting progesteron, etc.	For early determination of cow pregnancy
Amino acids and their derivatives	L-asparaginase (with the enzymatic procedure)	D-amino phenylacetic acid for a large-scale production of the synthetic antibiotic ampicilline
	Amino phenylacetic acid (with the enzymatic deacilation)	
Nucleic acid and its derivatives	RNA, small molecular DNA, Hydrolysis products, Yeast ATP	The compounds are of medical purposes for Republican use
Substances for biotechnological needs	Hydrolysates and extracts, Nutrient media, Buffer substances, Indicator paper, Sorbents	

Today, the potential of Latvian biotechnological sciences in total scientist number is estimated to be about 800 people. The amount of developed items makes 7 billion rubles a year. Worth mentioning here is a close cooperation of Latvian biotechnologists with Institutes of the USSR Academy of Sciences, Institutes of other Republics, the Branch Scientific Research Centres. Scientists of the Republic publish about 150-200 papers and defend about 30-40 author's certificates a year. Each year there are organized 3-4 conferences and symposia on various biotechnological questions. Most significant monographs and collected articles of the last 10 years are given in the List.

Biotechnological Productions

Latvian biotechnological industry today is represented mainly with classical biotechnological productions. A great contribution to the Republican economy is made by the fermentation branch—beer, ethanol, wine (especially champagne) and baker's yeast production, as well as the popular "Black balzam" producing firm "Riga's Balzams". In Riga, there are four breweries which employ the traditional technology, however a change of installations for automating and computerizing the processes is necessary. The same is to be said about ethanol and fruit-berry wine, and especially baker's yeast productions. In the Republican countryside, at the agricultural firm "Lacplesis", at Bauska, Tervete and other places there have been organized little country breweries. Many farms have fruit-berry wine productions.

Comparatively modern is the production of champagne by the reservoir ("Acretofor") procedure. The Experimental Plant of Biochemical Preparations of the Institute of Microbiology of the Latvian Academy of Sciences is a leading enterprise in the citric acid production in the USSR. Citric acid is produced from molasses by the surface procedure. Here, they are continuously selecting productive strains and obtaining seed material—starter culture, to meet the requirements of the whole USSR and many other countries. The submerged fermentation of citric acid in both molasses and hydrocarbon nutrient media has been worked out (together with the Institute of Physiology and Biochemistry of microorganisms, USSR Acad. Sci.). The producers and technologies have been patented and licensed in many countries. This plant has also developed a technology of itaconic acid production employed at the "Biolar" association at Olaine. The Experimental Plant of Biochemical Preparations has also mastered the isocitric acid and gluconic acid productions, as well as the production of organic acid salts. In the territory of the Experimental Plant of Biochemical Preparations there is located a depot of pilot and semi-industrial installations belonging to the Institute of Microbiology, which is used to master the production of various new microbiologically synthesized preparations, amino acids, enzymes, phytohormones, polysaccharides, etc.

The Experimental Plant of the Institute of Organic Synthesis of the Latvian Academy of Sciences has inherited the production of antibiotics, being the first in the USSR to initiate the production of penicillin, nistatine, grizeophulvine and other antibiotics. Here they instill antibiotic, enzymatic and chemical modifications, produce also L-asparaginase, hormones and other compounds including ones with recombinant bacterium strains. However, in the future, a major role at this Plant will be allotted to the chemical synthesis of compounds, especially the production of pharmaceutical means.

The "Biolar" association at Olaine has mastered the microbiological production of itaconic acid, the production of yeast nucleotides, ATP, L-amino acids, numerous enzymes of microbial, plant and animal origin, as well as biotechnological production of various biochemical reagents (see Table 3).

The agricultural firm "Lacplesis" specializes in the biotechnological treatment of agricultural raw material, including the treatment of apiculture products.

The Livani Experimental Biochemical Plant since 1970 produces lysine feed concentrate and vitamin-amino acid premixes. The production technologies were developed with the Institute of Microbiology participating. The total lysine production yield is about 3,000 t a year. The concentrate is produced in liquid and dried forms and beside lysine it contains bacterial biomass, riboflavin, bethaine and other valuable feed components.

In the production laboratories of the complex "Latvian Biotechnology" namely Cell-free Biosynthesis and Plant Cell and Animal Treatment By-products, they obtain enzymes, hormones, other proteins and products, ginseng extract, etc. In the agricultural firm "Uzvara", they have mastered the production of apple vinegar, fruit-berry wine, green mass feed protein, as well as starch-containing feed matters by microbial proteinization. At the "Ogre" farm bioreactors have been installed for the pig farm liquid waste methane fermentation to obtain biogas and valuable liquid fertilizer.

Potato propagule recovery and multiplication by the meristem technique is done at the Priekuli Selection Station, at the agricultural firm "Adazi" and that of flower—at the Ogre Meristem Laboratory (and at the Botanical Garden of the Latvian Academy of Sciences and the Latvian University), and fruit-trees at the Latvian Agricultural Academy. Biotechnological procedures have been widely applied in dairy industry which, since before World War II, can be proud of a high quality production. A specialized laboratory prepares and supplies dairy plants with starter cultures for the sour milk product and cheese production.

The production of many veterinary preparations has been concentrated at the enterprise "Sigfarm". Here they have mastered the production of prophylactic and therapeutic preparations, including acidophyllic bacpreparation and other different veterinary products. The

production of the fodder yeast has been organized at the Sloka Celluloze Plant on the basis of the sulphite slag, the yearly yield being 1,800 t.

Biotechnological enterprises of the Latvian Republic yield products that are very important for the economy. A programme has been elaborated organizing new scientifically rich raw material and energy-saving technologies for the benefit of health and environmental protection, the development of agriculture and industry.

Development of Biotechnology in Latvia

In order to find and ensure new resources for progress in the Republican economy within the time period of 1991-1995, it is obligatory to develop biotechnology as an interbranch science. It is planned in the following aspects:

Gene engineering. Foundations are elaborated for producing protein compounds required in the national economy and medicine with the help of gene and cell engineering methods. The development of antibodies and technologies for the needs of diagnostics and immunotherapy.

Plant tissue and cell engineering. It is planned to develop technologies of obtaining agricultural plants, fruit trees, ornamental plant meristems and protoplasts with the aim to select new highly productive and resistant sorts.

For a faster selection of cereals there have been worked out the bases of an embryo culture technology, for the first time the development and instillation of a transgene plant breeding technology has been envisaged. The development of a plant tissue culture technology will provide new resources—plant tissue biomass and product—production in industrial conditions.

Animal cell engineering. Theoretical and technological bases of embryo transplantation are being worked out with the purpose to organize a Republican embryo transplantation system for breeding highly productive resistant cattle and other domestic animals.

Food biotechnology. Investigations aimed at working out ecologically pure food industry technologies and products, the production of new sweeteners (invertsyrups, fructose) and their application development and instillation into the food industry, the development and instillation of a range of new dried and liquid drink, the production of food stabilizers, aromatizers and dyes and possibilities of a maximum use of meat, milk and other resources are envisaged.

Medical biotechnology. Within the subprogramme it is planned to do investigations

—with the purpose to develop and instil immunodiagnostic procedures into practical medicine;

—investigations aimed at the development of new prophylactic and medical means and their practical application, such as viral cultures with an anticancer activity, proteini and polysaccharide immunoprotectors (dsRNA, levan, etc.).

Agricultural biotechnology. Efficient resource-saving, ecologically pure technologies of agricultural production based on an employment of biological and biotechnological appropriateness, the construction and building of automatized and mechanized small farms are worked out.

The system envisages the production of milk, meat and field-crop and horticultural products harmless to health.

Ecological biotechnology. Theoretical foundations and methods of the control of genetic material (plants, animals, people and microorganisms) upon its critical pollution, biodegradation by toxic compounds are worked out. Technologies for waste water treatment also will be developed.

Animal feed biotechnology. The selection and production of biotechnological bases of feed additives—proteins, amino acids, vitamin complex, biological silaging means, biostimulators, etc. to enrich local feed resources and feeds are the main activities. Biological methods of preserving food products and animal feeds are worked out.

Biological means of plant protection and biostimulators. Development of new, and improvement of the existing, ecologically safe plant protective and biological means are planned and development and instillation into industry and agriculture the methods of obtaining and employing plant biostimulators.

The task is to provide high yields of crops from closed and open areas, and gain new resources for export.

Biotechnology of organic acids. The selection of highly yielding producers and the production of organic acids, such as citric, isocitric, itaconic, gluconic, ketogluconic and others, for the needs of food industry, technical, medical and special requirements is done. The development of surface and submerged cultivation technologies from carbohydrate and hydrocarbon sources is envisaged.

It is also envisaged to design new citric acid productions to eliminate the food industry deficiency in the Republic and to organize export of this product.

Bioengineering. It is aimed at elaborating theoretical and technological bases for designing biotechnological apparatus: fermentors for the microbe, plant tissue culture and animal tissue cultivation; biotechnological equipment and technical means for measuring the mass exchange intensity in technological processes and other purposes.

It was planned to design an experimental production of first-rate fermentors with a parallel optimization of

biotechnological and other mass exchange processes and a minimization of the energy consumption.

Enzyme biotechnology. Deals with the development of technologies for the production of enzymes for the needs of food industry, human and veterinary medicine, animal feed, etc. from microbial, plant and animal material and methods of their instillation.

Veterinary biotechnology. Aimed at the designing of biotechnological methods and technologies to obtain veterinary preparations of a new class:

—preparations for recovering inproductive functions and embryo transplantation;

—preparations for the regulation of metabolism;

—immunoprotectors (vaccines, protein and hydrocarbon compounds);

—complex compounds of natural substances and anti-inflammatory compounds;

—diagnostical means.

Biotechnology of biofertilizers. Develops various solid and liquid biofertilizers for closed and open areas. It is envisaged to organize and design a specialized biofertilizer centre.

For the above-described investigations and productions it will receive financial resources from both Republican budget and treaties. To ensure a progress in biotechnology in the near future, it is necessary to provide a biotechnologization of the existing Institutes, as well as to organize an Institute of Molecular Biology, a Biological Complex at the Institute of Organic Synthesis and to construct a Bioengineering Block with workshops at the Institute of Microbiology. A modernization of experimental productions should be realized, new small enterprises, including cooperative enterprises and production laboratories should be developed.

The further development of biotechnology is unimaginable without wide international scientific or technical cooperation, especially among the Baltic states.

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Trends in Bioengineering in Latvia

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[Article by U. Viesturs, Latvian Academy of Sciences, Institute of Wood Chemistry]

[Text] To carry out any biotechnological process, special equipment is needed. Moreover, the research equipment, especially an analytical one, is enormously manifold. The industrial-scale equipment is quite specialized yet with many analogues to that which is used in chemical and food production. To maintain the process, equipment for measurement and control are necessary, lately—computerized.

All bioengineering equipment may be divided according to its function into:

1—research analytical;

2—research technological (laboratory ware, reactors, disintegrators, a wide range of devices for extraction, purification, and concentration of final products);

3—technological pilot or semi-industrial and industrial scale, including those for:

3.1—upstream processes;

3.2—fermentation (aerobic, anaerobic, batch, feed batch, continuous, etc.);

3.3—fractionation of fermentation products (separation, disintegration, distillation, etc.);

3.4—extraction, purification and concentration of substances needed (sedimentation, ionic exchange, chromatography, crystallization, and many other processes of chemical engineering);

3.5—measurement and control of the process implying the computer. It is necessary to mention that all individual apparatuses, machines and units should be complete with measurement and control equipment. However, in practice there are still cases when workshops or plants are assembled according to individual projects.

In this case, theoretical basis for production of the equipment are constructions analogous to those of chemical engineering.

There are chairs and institutes, as well as companies of chemical engineering which are concerned with biotechnological equipment, yet there are few specialized ones and they produce fermentation techniques mainly for research. Still, industrial equipment in the world, in our country and in the USSR are elaborated and produced mainly by chemical and food engineering.

Lately international conferences on chemical engineering show interest in biological engineering as a rule.

We have made reviews on general problems of bioengineering [6; 9; 11; 13; 66; 73; 76], collected information on our new works [21; 26; 28; 36; 47; 57; 60; 74; 75], generalized our experience in monographs [4; 10; 14; 38; 49; 51; 52; 59]. The present review deals with the knowledge of several new, rarely discussed studies in biological and chemical engineering, as well as touch upon problems to be solved in the future.

I. Novel Research Equipment

The research equipment for measurement and control is worked out in two direction groups:

—original design;

—parallel production of the equipment available on the world market [53] (parameters to be measured are known, there are analogues of the equipment, too) with some advanced technical characteristics.

The first group mainly consists of apparata, which are protected by the authors' certificates (patents), and they are designed to complete the biotechnological equipments FU-8 and FU-30. They include apparata for foam control from PAP-1 to PAP-8 and AIPP-2; pH controllers from ARKO-1 to ARKO-6, redox potentiometer with a depolarizer and some other [25; 27; 28; 31; 39; 58; 61].

The stirring intensity meter is worked out [65], which represents a system of piezoelectric sensors with corresponding data processing. Detailed values are:

—kinetic energy of medium flow fluctuations E;—energy dispersion S_E;—dispersion variation V_S.

The calorimeter for heat release measurement of cultures in bioreactor under "on-line" conditions is elaborated [75].

Producers are: Special Design Office of Energetics Engineering (SDOEE), Institute of Physical Energetics; Special Design Office of Scientific Instrument-making (SDOI),

Institute of Polymer Mechanics [34]; Engineering and Technology Centre of the Latvian Academy of Sciences and Special Cooperative Firm (J. Vanags et al.).

The second group includes: dissolved oxygen IpO_2 concentration (partial pressure) measuring instrument, temperature controller, peristaltic pumps with monitoring units, stirrer shaft revolution velocity regulators (various modifications), devices for electric motor capacity measurements, etc. Producers—above mentioned.

Recently the cooperative company "Labotek" (V. Bankovsky et al.) started to produce the equipment of the second group. The company offers biotechnological laboratory- and industrial-scale equipment, including:

1—set of instruments IFKO for small laboratories of virus diagnostics by immunofermenting method (ELISA):

1.1—shaker for platres—IFKO-1; 1.2—microplate photometer (uniskan)—IFKO-2; 1.3—plate washer—IFKO-3

2—shaker for test-tubes—VP-50

3—platform shaker with general-purpose fixing mechanism for various devices, vessels and supports, adapters for Ependorph test-tubes (1.6 ml)—IFKO-2P

4—shaker for flasks of Erlenmaier—IFKO-1K

5—mierofugues for Ependorph test-tubes—M 1201

6—device for enzymatic DNA amplification with thermostable DNA polymerase—PEA 3001

7—eight-channel peristaltic pump—PN-8

8—electronic thermoregulating unit with sterilizing temperature sensor and outlet to heaters (up to 1.5 kW)—BRT-600

9—tachometers with a fixed set and digital display for adequate biotechnological equipment assembling—TED-1001

"FFERM"—the new fermentor used for experiments on the modern level has been developed by scientific research and production firm "BITEC" (A. Tjuterev et al.).

II. Equipment for Laboratory and Pilot-Scale Cultivation of Microorganisms

The Institute of Microbiology in cooperation with SDOEE has elaborated a number of modifications of appliances for laboratory-scale cultivation of microorganisms [6; 10; 34; 66], which, apart from our country, are successfully used in Czechoslovakia, Yugoslavia, Bulgaria, Germany. A new generation of these appliances is being elaborated (J. Vanags et al.), that will differ by advanced technical characteristics. In cooperation with IrkutskNIIHIMMASh and Scientific-Industrial Association "Promavtomatika" [34; 58] a pilot-scale biotechnological device is being worked out with the 1 m^3 fermenter. Intensive, yet shear-safe stirring system is elaborated [60; 67; 72; 74], which is in set with the described appliances (in detail—below).

The equipment for own use is elaborated and improved in almost every plant or institute; where it is necessary for basic work (Scientific-Industrial Association "Biolar", Livani Experimental Biochemical Plant, institutes of the Latvian Academy of Sciences and Ministry of Agriculture, University of Latvia, Riga Technical University etc.).

III. Equipment for Shear-Sensitive Culture Growth

With the appearance of a number of new products, of protein nature first (monoclonal antibodies, gene-engineering proteins—antigenes of AIDS virus, lymphokins, interferons, plasminogen activators, superoxidismutase etc.), equipment for their production becomes more complicated and manifold. One of the dominating tendencies is to work out an equipment, which ensures minimum shear effect on biological agent at intensive stirring (intensive mass transfer at phasetransfer liquid—solid). Presently these problems are solved for mycelial cultures [6; 61; 74], at the stage of elaboration—for tissue cultures. Mycelium-sparing constructions of the stirring systems in 0.005 - 5 m^3 bioreactors are elaborated (M. Rikmanis et al.). Microbiological fungicide "Trichodermin" (A. Apsite et al.) is becoming popular, the production of which enabled the bioreactor just of this—counterflow stirring system. Biochemical, morphological, etc. reactions of microbe populations according to the intensity and quality of stirring are being studied [62; 74]. The phenomenon of turbohypobiosis is defined and approbated [46]. Elaboration of novel carriers has started: scientific and industrial association "Biolar" has worked out and produces "Citolar" and immobilized biocatalysts for cultivation of surface-depending tissue cells of animals based on it. The Institute of Wood Chemistry—carrier "Meripor" for meristem cultures (A. Treimanis et al.).

IV. Industrial Bioreactors

Existing constructions of bioreactors are analyzed and their classification is elaborated [10; 12]. We tried to answer the traditional question: which apparatus is better—one with a mechanical stirrer or that with energy introduced only by aerating gas [10; 71; 72].

As it was already expected, we came to a conclusion that each construction serves its own purpose. However, some dominant points are convincing.

Reactors with a stirrer (with energy introduced with liquid and gas phase—Group I) are more universal. However, certain difficulties arise in the USSR at technical solvation of shaft sealing and its revolution velocity varying. Not more than 100 m^3 constructions are adjusted. The analysis proved [12], that at appropriate technical execution of stirring systems, these bioreactors are in no way inferior to other classification groups as to

the specific energy consumption. For example, our counterflow stirring system (p. 3 above) is among energetically effective ones [61]. These bioreactors can supply the minimum need of aerating air (even 0.2 - 0.3 v/v.m.), that is exceptionally important in acute ecological situation, as it makes air pollution minimal (minimum outlet of cultivated microorganisms).

The equipment with energy introduced only by aerating gas (Group II) is much simpler in design. Usually specific energy consumption is lower, however, there are exceptions (above). They are limited in stirring intensity (no more than 4 - 4.5 kg O_2/m^3 x h), suitable only for low viscous mediums and unicellular cultures. Mediums are strongly foaming because of the high rate of air consumption. A number of solutions are proposed to limit foam-formation [25; 27; 28; 31; 69] and, consequently, to reduce environment contamination.

There is another possibility for the reduction of contamination—repeated utilization of air. This is realized in the so called three-chamber fermenter [21; 56], which, apart from reduced specific air consumption has also a number of technical and economic advantages.

To cultivate bacteria producers (lysine etc.) in collaboration with IrkutskNIIHIMMASh a number of 100 - 300 m^3 bioreactor constructions are worked out [10; 21; 40; 72], including the above mentioned three-chamber one, which are being presently introduced into production (V. Krikis et al.).

Group III of the classification—bioreactors with energy introduced with liquid phase only—is characteristic with high local stirring intensity, accordingly problems of energy dissipation (medium homogenization) arise and they are not suitable for shear-sensitive cultures in principle and viscous (especially insoluble substrate containing) mediums.

Every plant works on completion and improvement of necessary bioreactors making use of accessible equipment from other branches. Fermenters with stirrers are made from chemical reactors of suitable working volume, driers are non-conventional, purification and concentration equipment is assembled from accessible suitable devices, as well and adjusted in the plant.

The problems of the industrial equipment for biotechnology in the USSR are analyzed [30].

To conclude the review on bioreactor studies (chapter 1-4), it is necessary to mark, that tendencies of their development in the world are considerably wider than our possibilities:

1) systems with biological agent immobilization become more widespread, correspondingly—biocatalyst reactors, including those with a mobile carrier;

2) membrane (hollow fiber) bioreactors, with mobile membranes, become very popular;

3) special bioreactors are worked out for growth of tissue cultures, plant cells included;

4) almost all elements of bioreactors—aeration and stirring systems, shaft sealing, air filters, batchers, sensors and signal processing systems etc.—are being improved.

V. Gas Analysis and Instrument Sets for Gas Balance Method

Monitored cultivation of microorganisms needs information on parameters of two classes:

a) depicting cultivation conditions (t, pH, eH, substrate concentrations etc.); and

b) depicting cellular metabolism—processes of cell metabolism, mass transfer with the environment and intracellular processes.

One of the second-class parameters which can be measured technically is reflecting the respiration intensity of microorganism cultures.

The measuring of them in absolute values can be carried out most reliably on the basis of gas balance method. The essence of this method is in the direct control of O_2 and CO_2 concentration in inlet and exit gases, of aeration gas consumption, volume of fermentation medium (or biomass quantity). On the basis of these values, specific rate calculation of O_2 consumption and CO_2 discharge can be carried out.

or

where Q_{O_2} -- rate of O_2 consumption, mol/l·h;

q_{O_2} -- specific rate of O_2 consumption, mol/g·h;

$C_{O_2}^{inlet}$, $C_{O_2}^{exit}$ -- oxygen concentration in inlet and exit gases;

$q_{n.c.}$ -- gas consumption, reduced to normal conditions;

V -- volume of fermentation medium;

X -- biomass concentration.

To realize the gas balance method, the control desk for gas analyzers PGA-2, PGA-3 is worked out using the equipment, produced industrially in the USSR [3; 10; 48]. It includes gas analyzers for oxygen and carbon dioxide determination, gas volumeter, and also a recording device for information registration.

The control desk for gas analyzers is meant to complete both laboratory and industrial-scale bioreactors.

The use of quantitative information on microorganism culture respiration intensity made it possible to work out a number of original methodical approaches for research purposes:

1. Determination of oxygen solubility in fermentation mediums [47].

2. Determination of oxygen mass-transfer [3].

3. Pulse method for steady state cultures [1; 2; 48].

4. Determination of energy effectivity of microorganism metabolism.

5. Quantitative determination of the limitation degree of cultures [2].

Owing to the fact that information obtained by gas balance method is effective and has a quantitative connection with the physiology of microorganisms, it can be successfully used for biosynthesis process monitoring.

The conception of mass and flow balance in fermentation process is elaborated (J. Shvinka, L. Baburin et al.), which allows an increase in the effectivity of these processes in the main parametres (outlet, velocity, productivity). The conception is realized in working out various methods of monitored cultivation for a number of producers (Br. flavum, Azotobacter, C. utilis etc.).

Methods are protected by authors' certificates (patents), approbated and partly introduced into industry.

Fig. 1 shows an example of an industrial process of lysine production with feed-batch, making use of the above described methods.

VI. Biogas Reactors

A technology of manure fermentation for the utilization of pig farm wastes is worked out (V. Dubrovskis et al.) [8; 16; 17; 18; 50], including the 100 m^3 bioreactor design for anaerobic methane fermentation (figure not reproduced).

Technical Characteristics of the Bioreactor

Total volume	100 m^3;
Heat carrier	water heating pipe φ 76 mm;
	length 143 mm;
Electric drive capacity	4.3 kW, velocity of stirrer shaft—8.37 rpm;
Mass	14 t;
Overall dimensions	14,225 x 3,980 x height 6,085 mm.

The delivery set includes devices for level regulation, pressure control, etc.

A technology and equipment for utilization of poultry wastes is being elaborated (V. Dubrovskis et al.); in particular—a bioenergetical set for the poultry farm "Iecava", Bauska region.

Raw material	—droppings—222 t per day.
Output	—manure—89 t per day;
	—liquid manure—133 t per day;
	—biogas which can be transferred into electrical energy—1260 kW/h, heat energy—1.58 Gcal/h.

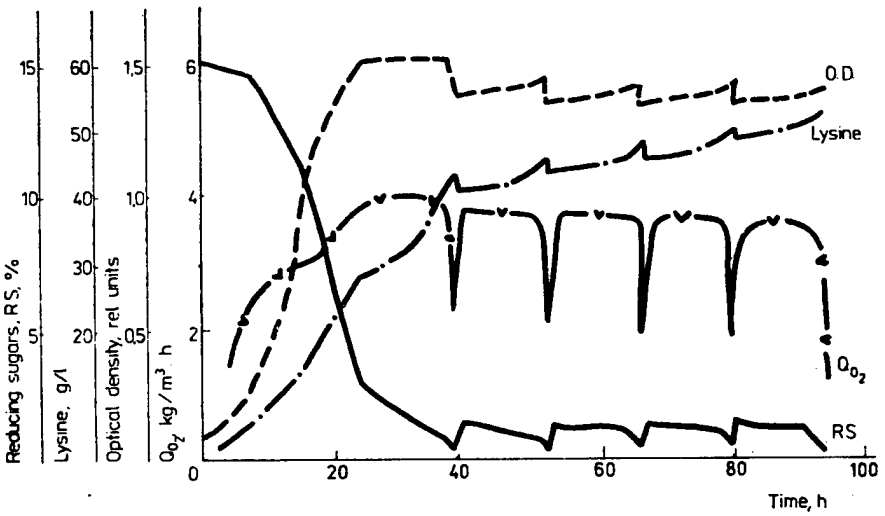

Fig. 1. Dynamics of feed-batch (semi-continuous) lysine biosynthesis process in 100 m^3 bioreactor of Tripolsk Biochemical Plant with feed-batch control as to respiration activity of the culture. Specific product yield (kg/m^3 x h) increases up to 30 percent.

Studies on pulp and paper industry waste degradation by methane fermentation have started (J. Zandersons, V. Dubrovska et al.).

VII. Dehydration of Microbial Culture Liquids

The Institute of Microbiology, Latvian Academy of Sciences, has developed hygroscopic microbial concentrates theory (J. Laukevitz et al.) [63; 64].

Concentrates of a number of microbiological synthesis products for animal feeds such as amino acids (LFC), vitamins, fermented and bacterial preparations, the bulk of the components of which comprises water-soluble extracellular part, possess a specific set of properties, particularly, increased hygroscopicity and thermoplasticity, that causes certain technological difficulties both at the final stage of production—dehydration of culture liquids, and at the application of dry trade forms in centralized feed production. For such preparations a method of structurization by dispersive carriers or sorbents is purposeful, the essence of which lies in drying material disposition in the pore space of the carrier particles.

At structurized preparation production the degree of sorption volume of the carrier determines the stability level of mechanical properties of the system (final product).

Lysine feed concentrate (LFC) is a typical example of the product of this class.

Our studies in structurization processes—LFC drying allowed to work out a number of novel technical solutions, increase the l-lysine content in the final product, preserving practical stability of its structural and mechanical properties, as well as to intensify the LFC drying process with the simultaneous reduction of energy consumption.

A dryer of fluidized bed is worked out and used for LFC production (J. Bojars et al.) at the Livani Experimental Biochemical Plant, and experimental dryer of vibrofluidized bed at the Experimental Plant of Biochemical Preparations, Institute of Microbiology, Latvian Academy of Sciences.

In recent years dehydration problems of similar products are proceeded at the Chair of General Chemical Technology, Riga Technical University (G. Smirnov et al.). The advanced technology is elaborated, including preliminary preparation operations of structurized component, its capillary impregnation by culture liquid in vacuum and double-stage drying process, carried out in combined dryer of non-conventional construction. On the first stage of it, structurized mixture dispersing and material particle drying is realized; on the second stage—material drying in the sprayable aerovibrofluidized bed.

Under these conditions the scale-up of l-lysine relative content in LFC for 13-15 percent is ensured, maintaining its practical stability. Specific moisture removed during the drying process increases 1.9 times at a considerable (1.5 times) energy consumption reduction.

The Institute of Microbiology (M. Beker et al.) works on problems of anabiosis, problems of culture viability preservation during the dehydration and reactivation processes, in particular. Nevertheless, bioengineering solutions in this sphere are few, therefore the present review does not deal with this trend in detail.

VIII. Purification and Concentration of Fermentation Products

Fermentation liquid flow-sheets are manifold and depend mainly on the purpose of product application.

For instance, when using the active biomass of lactic acid bacteria Lactobacillus casei var. alactosus during green crop silaging (A. Klincare et al.) and microscopic fungus Trichoderma viride as anti-fungus and growth-stimulating preparation (A. Apsite et al.), it is necessary only to cool culture liquid below biosynthesis temperature at the end of fermentation. Partial biomass concentration by separation is possible.

Specially for hard-filterable biological suspensions a new dynamic filter construction with continuous sediment removal from the filterable surface is elaborated at the Scientific and Industrial Association "Biolar". The filter which rotates in suspension allows to realize processes of filtration, washing, stirring and extraction within the same suspension volume (J. Eglitis et al.).

Great experience is gained in concentrate forms of irreplaceable l-lysine amino acid production by concentration and drying the entire fermentation liquid (p. 7 above). However, this method, apart from many advantages, has shortcomings as to physical and chemical characteristics of the preparation and danger of the formation of biologically inactive lysine form.

In cases of intracellular metabolites discharge from biomass, or extracellular from fermentation liquid, biomass must fully separate. The degree of biomass separation, as well as of other suspended particles and colloid substances determine the quality of the product. Thus the separation of biomass with subsequent microfiltration increases the specific activity of spray-dried lipolytic preparation 2 - 2.5 times as compared to single-time separation (R. Are et al.).

The combination of concentration processes, including vacuum evaporation, sedimentation, membrane and sorption processes, on the first stages of substance discharge leads to multiple reduction of the processed volumes. Sorption of plant growth stimulator fuzikokcin by activated coal reduces the volume 5 - 6 times (A. Logina et al.), lysine sorption by cationite KU-2 8 - 3 times (R. Are et al.), sedimentation by organic levan polysaccharide—2 times (E. Samulevich et al.).

A technology of ionic exchange l-lysine extraction on strong-acid cationite KU 2x8 is elaborated. Lysine sorption from acidated fermentation liquid with subsequent

elution by ammonia water reduces the original volume 3 - 4 times, and at crystallization 92 - 96 percent l-lysine monochlorhydrate is obtained. This technology successfully combines the production of crystalline amino acid with the concentrate preparation.

More selective methods are used at next stages of purification, as affine chromatography, membrane fractionating etc. The Engineering and Technology Centre, Latvian Academy of Sciences, intends to develop a membrane technology.

Fractionating of double-stranded RNA raw preparation through the hollow fiber VPU-100-type membrane allows at 0.7 - 0.8 m/sec flow rate to reduce the influence of concentrate polarization and to separate low-molecular inactive fraction of dsRNA (A. Iskanderov et al.).

As it is shown by the above described examples, processes of purification and concentration are highly complicated and manifold. Scale-up of laboratory methods of discharge and purification of biopreparations often demand considerable technological studies depending on properties of initial material and the desirable degree of purity of the end substance.

IX. Purification Equipment for Communal Sewage

Purification installations of Riga are being built. Flocculants are needed to exploit them. Joint venture "Luriflok" (JV) is formed together with the partnership from Germany and scientific and industrial association "Ekocentr" from Latvian side (A. Grinbergs et al.). Main tasks of JV are:

—elaboration of reagents and technological processes for the purification of drinking water and sewage;

—production and realization of reagents, including flocculants for dispersion system processing;

—elaboration of technology and design of purification installations.

The construction of experimental shop on the territory of Riga purification installations in Bolderaja is finished, and first tons of flocculant are produced; the product will be realized in Riga, as well as in Tallinn, Leningrad etc.

Organization of normalization (preliminary purification of concentrate sewage) is important for separate enterprises (galvanic shops, varnish and paint production, detergents, leather processing etc.) before Riga purification installations are put into operation. Specialists from the Riga Technical University, "Luriflok", Institute of Microbiology etc. take part in this enterprise. Thus, for instance, "Luriflok" inspected local purification constructions of the fishermen's collective farms, and the first agreements were signed.

A device for condensate sorption from fish-smoking shops using woodwaste or coal, which is burned or regenerated together with waste, is elaborated at the Institute of Wood Chemistry (E. Aunins et al.).

The Institute of Microbiology (A. Upitis et al.) offers the equipment for:

—feed production sewage bioutilization (agrofirm "Uzvara", Bauska region): raw material—feed production sewage 3 m^3 per day;

—produce—40 m^3 biogas per day, destruction of COD sewage to 70...80 percent;

—biogas energy transformation—combined;

—electric power and heat production;

—sanitation of sugar production sewage (Jelgava Sugar Plant): 135 m^3 bioreactor, horizontal, sectional; sewage—130...200 m^3 per day; biogas output—250...300 m^3 per day; COD destruction up to 85 percent.

"Anaero-S" process:

—milk production sewage sanation (Rezekne Milk Cannery, Kaunaste village): 100 m^3 bioreactor, chamber, sectional; sewage—up to 75 m^3 per day; biogas—up to 30-40 m^3 per day; COD destruction—up to 96-98 percent.

"Anaero-M" process:

—organic waste bioutilization of a farm (bioreactor MI-30): total volume of bioreactor—30 m^3; working volume—25 m^3; productivity—of manure and faeces sewage—up to 1.8 m^3 per day; of biogas—up to 50 m^3 per day (32 l per day as to oil equivalent).

The improvement of sewage purification equipment, especially due to pressing ecological problems in the Republic, is an extremely wide sphere, which deserves a special review. What is described above is only an example of the work done by the author and his closest colleagues.

X. Equipment for Chemical- and Bioconversion of Photosynthesized Raw Material

The following biomass (renewable raw material) conversion schemes are known:

1) gasification, then production of H_2, NH_3 methanol, formaldehyde, methane, hydrocarbons;

2) pyrolysis with coal, oil-like products, gas production;

3) dilution with the production of chemicals;

4) sugar refining (hydrolysis, preprocessing)—production of improved feed, glucose, molasses, xylose, furfural, lignin, with further production of ethanol and other bioproducts;

5) fractionating—production of cellulose and its derivatives, paper, fibers, sulphate and sulphite alkalines, lignin, water extracts, chemicals, bioproducts.

According to the two last directions, the Institute of Wood Chemistry, Latvian Academy of Sciences, has elaborated non-conventional technologies and equipment, which, apart from the other, clearly demonstrate the connection between the chemical and biological engineering.

X.I. Technology and Equipment for Chemicomechanical Straw and Other Cellulose-Lignin Waste Processing

Technologies for alkaline mechanical straw treatment using non-conventional equipment have been developed, permitting flaky feeds to be obtained [7; 54; 55; 68]. Non-conventional equipment is an original design of the main apparatus which consists of an auger feeder and disperser-mixer. Three modifications of the apparatus are elaborated: ADM-290, ADM-250, ADM-160.

Technical Characteristics of the Apparatus

	ADM-290	ADM-250	ADM-160
Capacity, t/h	1.0	0.9	0.5
Auger feeder diameter, m	0.29	0.25	0.16
Auger revolution, rpm	72	180	200
Drive capacity, kW	200	132	100
Mass, t	17	5	4
Overall dimensions, m	6.8x2.2x1.8	6.3x1.1x1.0	4.6x1.0x0.9

All three modifications of the device provide a perfect mechanochemical straw treatment. The elaborated technology is wastefree and intends the application of sodium-hydroxide or ammonium water solution. For preliminary straw chopping, conventional equipment can be used.

The apparatus ADM-160 is produced by the Special Design Office of the Institute of Wood Chemistry. Technical documentation on ADM-250 and ADM-290 is elaborated.

A similar device is tested for straw acid hydrolysis. It can be used for waxy-ripe crop, grain, rape-seed, etc., feed treatment.

In conclusion, the universal nature of the described devices must be pointed out: they are fit for the most variegated material processing (waste mainly)—products of photosynthesis. The obtained products may be used as feed for ruminants or raw material for biotechnology [7] and in enzymatic cellulose hydrolysis, studies in wood processing at paper production have started.

There is one more example. Hydrolysis of slightly decomposed peat can be carried out within similar equipment, too. Mechanochemical destruction of peat components takes place in a continuous-action non-conventional appliance, where during 20 - 30 sec water-soluble products are formed out of chopped peat, preliminarily mixed with concentrated sulphuric acid. Extraction of mechanochemical destruction products and resolving of oligomers into monomers is carried out in a special device. Fine dispersive suspension is formed, in which sulphuric acid is neutralized by alkaline agent. Any equipment of analogical application can be used for neutralization. The obtained suspension is decomposed by filtering into final solution, which contains monosaccharides, amino acids and water-soluble humine substances, and the non-hydrolyzable residual, which contains mainly humine substances.

Hydrolysates of the upper slightly decomposed peat, produced by this method on auger screw hydrolyser, substantially differ from other types of plant raw material hydrolysates. They contain about 2 percent humine substances of peat, which, in difference to substances of ligno-humine complex of other hydrolysates, in certain concentrations act as growth stimulators. Apart from that, they contain the increased quantity of additional feed sources—organic and amino acid.

Peat hydrolysates may be used as culture medium in microbiological synthesis, particularly—for SCP biomass production. The Institute of Wood Chemistry has elaborated technology for medium preparing and SCP growth on peat-based medium. A special SCP strain is bred, which is safe to high concentration humine substances, utilizes hydrolysate components very well and gives 63 percent RS biomass discharge.

Another way of peat hydrolysate use—its application as additive, stimulating microorganism growth on other culture-based mediums. Thus, adding 1 - 5 percent medium volume peat hydrolysate of Vjatka Biochemical Plant (USSR) production, discharge of SCP increases to 2 - 10 percent, but content of protein in them—to 2 percent (J. Gailitis et al.).

Possibilities of peat hydrolysate application in stock-breeding (stimulating feed additive) and plant-growing (seed sprouting and productivity of vegetable crops stimulator) [15; 29] are studied, too.

X.II. Mixers for Furfurol A. O. Products Production

Theory and practice of stirring, particularly, of solid and liquid materials are among the most important objects of study for chemical engineering. Three modifications of mixers for homogenization of small quantity liquids (catalysts) with the loose plant raw material were made (A. Kulkevitz et al.), Special Design Office, Institute of Wood Chemistry [20; 22; 23; 34].

Technical Characteristics of Mixers

	SM-400	SM-500	SM-500 (doublestop)	SM-600
Productivity:				
—mass (chips), kg/h	2,800	7,500	7,500	29,500
—volumetric, m^3/h	8	20	60	100
Auger-blade shaft:				
—diameter, mm	400	500	500	600
—number, pieces	2	2	2	4
—speed, rpm	50-60	60	70	80
Number of nozzles, pieces	2-4	4	6	6
Installed power, kW	7.5	11	15	44
Material	steel 12X18H10T			
Total mass, kg	1,100	3,400	4,400	5,600
Overall dimensions, mm	3980x1000x1470	4090x1280x1400	4190x1530x1460	4750x2335x1960

Application: SM-400, SM-500, SM-600—production of furfural, sugar, cellulose; SM-500 doublestop—production of furfural, sugars, agricultural animal feeds, substrates for biotechnology.

XI. Equipment for Agricultural Biotechnology

In the present-day situation in Latvia, priority undoubtedly is toward engineering for agriculture. However, on the basis of agrofirm "Uzvara" a. o. well-to-do collective farms, a number of studies of biotechnological character are carried out, which also need equipping: fermenters, evaporation, drying, centrifuges, special laboratory-scale equipment, equipment for meristem cultures, for embryo transplantation, for production of a number of food-stuffs, etc. These elaborations mainly refer to the second group (P. I), and the analysis of them within the limits of the present review is quite difficult.

Problems of Bioengineering in Chemical Engineering

The main problem for us, like in all branches of science and technology, lies in inconvertability of rubles. Because of this fact, to keep the world level of separate design (as it is used in the whole world), buying the rest, we must carry out parallel studies. In the USSR enterprises of the Minneftchimmash must work out bioengineering equipment, while the equipment for measuring and control is designed by those of the USSR Minpribor. However, the problem of complete deliveries (with the control assembly) is not solved in the majority of cases.

The world level (competitive) of a number of technological equipment units is not achieved. Among the most important are:

1. Complete sets for sterilization of culture mediums.

2. Exceptionally limited choice of membranes for air filters, purification and concentration of final products.

3. There are no safe sealings for revolting shafts. Industrial-scale drives with easy controller stirrer shaft revolting velocity are missing.

4. Set of complete sterile bioreactors is needed, including those of 100 m^3 volume.

5. Biomass disintegrators are missing (except elaborations of B. Fichte et al.).

6. Bad evaporation (for thermolabile substances) and drying equipment.

7. Purification and concentration equipment has a number of technical shortcomings.

8. Sterilizing sensors of signal information are almost always missing and computer possibilities are poor.

9. A number of analytical appliances, instruments and laboratory techniques are lacking.

In outline, the above mentioned with the exception of our above described elaborations (p. 1-10), refers to Latvia, too. Quite often license selling becomes considerably complicated, because of lack of proper equipment, or the participation of foreign machine-building companies is necessary (technologies of citric acid (R. Karklins et al.), lysine [38; 70], furfural [5; 24]). But, for instance, home production of crystallic lysine is not possible to solve for dozens of years already because of the equipment difficulties (ionic exchange columns etc.). In the Institute of Wood Chemistry there are examples of chemical processes, which cannot be introduced into industry because of the lack of adequate equipment or because of an extremely complicated elaboration and production system of the original one (wood, peat, a. o., hydrolysis by concentrate acids, lignin thermolysis, levoglucosan production, wood modification by ammonium [37; 45] a. o.).

Thus, the investigation of general processes of bio- and chemical engineering and, on the ground of this information, creation of the adequate equipment (partly competitive and a number of analogous to that available on the world market, because of the lack of hard currency) is still the most important task of the USSR [10; 34; 53; 76], Baltic Republics and Latvia in particular. In

spite of comparatively good achievements in machine-building in the Republic (Complex "Masinbuve", "Rigachimmash", plants VEF, "Radiotehnika", "Alfa"; Special Design Office of Energetics Engineering, Institute of Physical Energetics, Latvian Academy of Sciences; Special Design Office, Institute of Polymer Mechanics, Latvian Acad. Sci.; Institute of Electronics and Computer Science a. o.), the above mentioned refers also to the elaboration and production of control and monitoring equipment for biotechnology and chemical technology.

A good chance for the improvement of the present situation could be the construction and operation of the Bioengineering block (a staff of 110 people) at the Institute of Microbiology, Latvian Acad. Sci. This project would be realized more successfully by introduction of foreign business in the form of joint venture formation.

In this connection, there is one more problem. It is very difficult to fix the demands of biotechnologists with the possibilities of machine-builders. We shall explain it on the example of fermentation equipment.

On the one hand, in the regulations, for the realization of which the equipment is selected/produced, regimes are not defined precisely enough. There are terms: intensive stirring, an excess foam formation, etc. As a rule, data for heat transfer surface calculation, for drives and data on medium corrosion (for the brand of steel selection) and other characteristics are lacking, which are necessary for bioreactor engineering calculations. Data on shear-sensitive biological agents, that must determine the optimal stirring method (type of stirrer), are absolutely missing. At the same time chemical processes are characterized as considerably simpler.

On the other hand—technical characteristics of the bioreactors are not defined well enough, also.

We attempted to work out methods of preliminary bioreactor selection [10; 38], however, this task is still among the problems, which are not fully solved.

The author hopes, that M. Beker's review on classical biotechnology, together with the present article on the equipment, as well as several articles on specific, more narrow problems, will give the reader the full idea of the present-day situation in biotechnology and bioengineering in Latvia.

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Biotechnology in Lithuania Today

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[Article by A. Janulaitis and V. Naktinis, Institute of Applied Enzymology "Fermentas", Lithuanian Republic]

[Text] Biotechnological products and biotechnological production accompany man from time immemorial and are indispensable and inseparable from the functioning of society. In Lithuania this field of occupation has developed in the so-called classical fields of biotechnology such as the production of beer, alcohol, wine and baker's yeast.

Production of vaccines and simple means of diagnostics in microbiology began developing in the first decades of the 20th century, and in the end of the first part of it the enterprise producing medical preparations, insulin from animal pancreas included, began functioning. Yet the greatest part of biotechnological potential in Lithuania was created between the 1960s-1970s with the foundation of biological institutes of the Lithuanian Academy of Sciences and the Institute of Applied Enzymology "Fermentas", and with the setting up of plants.

Additionally, taking into account that the scientific capacities operating in the field of biotechnology exist also within the variety of specialized scientific research structures of medical, higher education, agriculture, veterinary and animal husbandry institutes, a whole representative conception of biotechnology in Lithuania can be formed.

The data and statements in this survey are based on the information, kindly presented to us by Lithuanian institutes involved in biotechnology. Based on alternative information sources we can state that the mentioned inquest embraces not less than 95 percent of Lithuanian institutes taking active part in biotechnology.

The aim of this short survey is not to inventory the activities of each separate institute but to describe the main parameters characterizing the potential of biotechnology in Lithuania. That is why organizations or scientific themes that are fulfilled today or a production that has been manufactured not mentioned in this survey should not be considered as ignored.

So, first of all, a few quantitative facts reflecting the potential of subjects of biotechnology in Lithuania. It is well known that the potential of industry of biotechnology as well as of any other sphere of production is most fully revealed by the scale of industrial production. Table 1 shows general data on the production of main products (dominating in their volume) of classical biotechnology in Lithuania. These enterprises-producers are usually not specialized in producing monoproducts. That is why the total number of enterprises producing classical production of biotechnology (24) is less than it may be concluded from the data given in Table 1.

Table 1. Large-Scale Manufacturing of Products of Classic Biotechnology in Lithuania (situation for 1990)

Description	Number of plants or institutes engaged in large-scale production	Total volume of annual production
Baker's yeast	1	4,300 t
Beer	7	more than 15 m dkl
Wine	1	0.1 m dkl
Vinegar	1	0.465 m dkl
Ethyl alcohol	6	2.5 m dkl
Enzymes for food industry, agriculture and for other technological needs	2	approx. 970 t (10 items)
Bacteric leaven for dairy industry	1	70,000 dozes
Fodder yeast	2	more than 5,000 t
Premixes	1	72,000 t
Furfurol	1	135 t
Pure preparations (reagents) of enzymatic origin*	1	more than 120 items
Preparates for therapy, prophylaxis and diagnostics from animal and plant	2	insuline, heparine, hormones from guman, porcine and bovine pituitaries, etc.—approx. 55 m dozes and more than 1,500 conventional liters of serum products

*This item covers also the enzymes used in genetic engineering, such as restriction enzymes, ligases, polymerases.

The list of products of modern biotechnology both in volume and the number of enterprises-producers is shorter. Today it limits itself only on turning out pilot plant-scale production. The main scale of the industrial manufacturing of products of this type is shown in Table 2.

Table 2. Large-Scale Manufacturing of Modern Biotechnology Products in Lithuania (situation for 1990)

Description	Volume of production	Plant or institute
Recombinant human a-2-interferone (substance)	1 m dozes	Institute of Applied Enzymology "Fermentas" (IAE "Fermentas")
Recombinant enzymes for genetic engineering	27 items	IAE "Fermentas"
Membranes with immobilized enzymes for biosensors	200,000 pieces	Institute of Biochemistry of the Academy of Sciences of Lithuania,
	approx. 1,000 cm^2	IAE "Fermentas"
Enzymatic biosensors	50 units,	IAE "Fermentas",
	1,000 units	Institute of Biochemistry of the Academy of Sciences of Lithuania (with "Sigma" enterprise)
Virus-free potatoe seed	approx. 45,000 plants	Voke Division of the Institute of Agriculture of Lithuania

It is necessary to note that in this case spheres closely related to modern biotechnology, yet not ascribed to it, such as manufacturing of synthetic materials with growth stimulating effect or other biological activity and the pilot plant-scale production of chromatographic sorbents, were not embraced. The production of immunological test kits fulfilled in 4 - 5 institutes on the pilot plant-scale should not be treated as being produced yet because of its small volume. So we can see that in reality only three institutes are involved in industrial manufacturing of products of modern biotechnology. It is worth noting that they are institutes possessing pilot plants.

The quantitative estimation of the potential of organizations involved in scientific research work or research and development (R&D) of biotechnology is shown in Table 3.

Table 3. Estimation of Total Potential of Research Organizations Engaged in Biotechnology (situation for 1990)

Plants and institutes, number	Workers, total	Research workers*, number	Annual budget, m rubles**
16	3,200-5,400	800-900	21-22

*Only those involved in biotechnology.

**Only for investigations in biotechnology and near-lying areas.

Bearing in mind all the relativeness and complication connected with the data chosen for estimating our scientific potential, we dare to admit that for the first step taken in acquainting with R&D of biotechnology in Lithuania it should be quite suitable. It would be necessary, perhaps, to show at least the fragments of what lies under such numbers as 800-900 of scientific personnel fulfilling yearly R&D works worth 21-22 million rubles. About 80 percent of the means allotted to this field go to four institutes—Institute of Applied Enzymology "Fermentas", Institute of Biochemistry of the Lithuanian Academy of Sciences, Institute of Botany of the Lithuanian Academy of Sciences and Institute of Butter and Cheese Industry. The Institute of Applied Enzymology "Fermentas" alone speeds more than 50 percent. Similar proportion or, perhaps, disproportion can be seen in the distribution of scientific personnel: 50 - 60 percent of scientists involved in biotechnology in Lithuania work in the four above-mentioned institutes while in all the rest, as a rule, there are only from several up to 20 - 30 qualified specialists in this field.

It is worth noting that great additional potential in fulfilling R&D in the field of biotechnology is "hidden" in the inner structure of the industrial enterprises of this profile, i.e., in the form of various laboratories and experimental departments.

Even not having exact data and having estimated the above-mentioned factor, we can assert that the number of active scientific personnel in biotechnology in Lithuania is 1,000 - 1,200.

It is evident that biotechnology as a branch of industry, engineering and science has accumulated good production basis and numerous scientific personnel in Lithuania.

While aimed at giving a comprehensive view of the level of potential of biotechnology in Lithuania it is necessary to show some of the qualitative facts. It would be purposeful to limit the characteristics of the structure of the main manufactured production and, speaking about R&D, the up-to-dateness, originality and the main tendencies of the carried out research should be estimated.

The analysis of the structure of industrial production reveals the amount of products manufactured for food industry (yeast, ethanol, vinegar, beer) produced in Lithuania is less than should be enough for home use (an exception, according to the data presented by the Institute of Butter and Cheese Industry, is the production of bacteric leaven for dairy industry). At the same time, enzyme preparations, both technical and pure, and preparations for medical use, as well as produced for export to the USSR mainly, and their need in Lithuania make up no more than 10 - 20 percent of the production volume. A similar situation tends to be in manufacturing in modern biotechnology where the tendencies of export to the USSR of recombinant medical preparations, enzymes for gene engineering and diagnostic means dominate. As to export for currency, it should be mentioned that it should be limited to a very small amount of products consisting mainly of enzymes for gene engineering and of semi-manufactured products of hormonal preparations from human hypophysis—somatotropine.

It leaves no doubt that the structure of production of biotechnology in Lithuania needs improving, first of all, expanding the production of products of first need for food industry. On the other hand, the spontaneously produced assortment of other products and the tendency of orientating to the market of the USSR should be estimated as a very favorable circumstance for the future of Lithuanian economy. As to the scientific research and development, we consider it impossible to estimate them in such a short survey without necessary examinatory argument. So we shall give only the most general statements.

First of all, if we analyze the momentary view only vaguely we shall notice that in the panorama of scientific research in biotechnology in Lithuania there is a characteristic mosaic of small themes and problems which are quite distant, from the point of view of research methods and the future practical usage. Still, having investigated more deeply, a consistent and versatile (especially bearing in mind that the development of biotechnology in Lithuania has not been coordinated in any way up till now), the existence of dominant reveals itself. No doubt it is the search and realization of diagnostic methods, reagents, means and systems based on the achievements in up-to-date molecular genetics, immunology, microbiology and biochemistry in medicine, agriculture, food industry and biotechnology itself. The majority of institutes in Lithuania working in the field of biotechnology

are occupied with this problem in one aspect or another. We should like to mention only the most important spheres:

a) enzymatic analyzers (biosensors) for medicine and biotechnology;

b) reagents (enzymes included) and analytic compositions (kits) for biochemical (photometric) analysis in medicine;

c) diagnostics on the basis of nucleic acids for microbiologic infection, for defining genetic status of organism in medicine, sanitary, food industry, veterinary and forensic medical examination;

d) various types of immunochemical diagnostic kits for medicine and agriculture.

On the other hand, it would be an inexcusable vulgarization to try to reflect the research gamma of biotechnology in Lithuania in such a schematic way. That is why it is a must to note as one of the most sophisticated trends of modern biotechnology, both technologically and methodologically, the creation of technology of producing recombinant human proteins for medical needs (interferons, growth hormones, insulins, etc.). It is unlikely as well that technologies of production of pure enzymes, those meant for gene engineering among them, should lose their urgency in the nearest decades. In the two spheres mentioned above, Lithuania has an undoubtable priority in East Europe. Great animal endocrinic material stock, on the one hand, and the created manufacturing basis of endocrinic hormonal preparations, on the other, create good preconditions, having introduced the up-to-date methods of protein purification and analysis, for raising the quality of produced preparation and for creating new, scarce products for medicine and veterinary. Research done in the field of polymer material biodegradation and oil spillage cleaning by the use of microorganisms are of no less importance and ecologic value.

In this survey the problems of biotechnology in Lithuania were barely touched upon. It is a topic to be discussed separately. And yet it seems necessary to focus the attention on the points that, in the nearest future if not today, will be the "bottle-neck" in the development of biotechnology as a branch of priority in the economy of Lithuania. Such points are:

a) dependence of industrial and especially scientific biotechnology on the imported materials and the necessary reagents and supplementary materials, packing included;

b) dependence on the imported biotechnological manufacturing and scientific-research equipment.

The potential of biotechnology in Lithuania today greatly depends on solving outside matters—searching and finding economic and organizational levers to create a reliable guaranteed background for biotechnology, a sort of infrastructure, understood as supplying materials and equipment of adequate quality. It is disappointing that having both biotechnological industry and qualified scientific personnel and the whole of knowledge and ideas in Lithuania, we are confronting the need to start from the foundation. And biotechnology is not an exception, for many things are to be built anew in Lithuania today.

Biotechnology in the Chemical Complex of Estonia

917C0428 Riga IZVESTIYA LATVIYSKOY AKADEMII NAUK in Russian No 12, Dec 90 (manuscript received 1 Dec 90) pp 98-102

[Article by A. I. Kestner, Tallin Technical University]

[Text] The transition to a market economy is accompanied by more than just administrative and legal changes of societal structures. It requires primarily a considerable improvement in the quality of the goods we produce. In all of industrial civilization, the essential, absolutely irreplaceable part of the economic complex is based on chemical techniques for converting substances. That group of substance conversion technologies (SCT) includes not only classical chemical technology, but also metallurgy, the pharmaceutical industry, and a number of sectors of the food industry, as well as, most certainly, industrial biotechnology. Not all divisions of the substance conversion technologies need be developed on a separate, bordered, economically independent territory, and for some SCT processes, the most efficient operation is that performed by large specialized enterprises that have a broad, often even global commodity circulation. On the other hand, a number of fine SCT processes are quite effective when done on a small scale, and they can also strengthen considerably the economic potential of a small state. To a great extent, that is true at present of the development of biotechnology.

In Estonia, the idea for the formulation of the concept of the development of the republic's chemical complex was brought to the fore by scientists. A temporary group was created at the Estonia Academy of Sciences Institute of Chemistry for the purpose of studying the issue and preparing documentation analyzing the situation and producing forecasts and recommendations. The director of the institute, Prof. Yu. M. Kann, was named head of the group, and Prof. G. Rayalo, his deputy. A conceptual document is now ready and available to specialists.

Included in the concept is the issue of the development of biotechnology. The leadership of the appropriate working group was assigned to the author of this article. The group included A. Yagomyagi, Yu. Kumar, and R. Vilu. The brief survey that follows is based on material assembled and assessed by that working group, but it also includes some personal, perhaps subjective points of view of this author. It should also be mentioned that working within the confines of Prof. Kann's creative

group was a separate group, headed by Academician M. Lille, that dealt with the production of physiologically active substances and with the pharmaceutical industry.

As we know, there is no complete agreement on the meaning of the term "biotechnology". Some scientists label as biotechnology, the goal-oriented alteration of the properties of living organisms—particularly, alteration that uses gene engineering and cell fusion—as well as operations involving cell and tissue cultures and embryos. In Estonia, a great deal has been done in that field. The evolution of that area is largely associated with the Estonia Academy of Sciences Institute of Chemical and Biological Physics and with the initiative of the institute's director, Academician E. T. Lippma. Great success has been achieved at Tartu University and at sector institutes. Extremely high-level research that is producing good results is being done at the Estonian Biocenter (in Tartu), under the guidance of Academician R. Willems. The well-known molecular biologist, Prof. M. Saarma, is now working as director of an institute in Helsinki.

Although this author gives high marks to the results of the work done by Estonia's scientists in that field, he does not consider himself qualified to provide an in-depth analysis of their work. For purposes of preciseness, he suggests using the term "technobiology" for the above-mentioned area involving the goal-oriented alteration of living organisms. The results of technobiology can be directly applied in agriculture (to produce new strains of plants and new breeds of animals), but in the main, its place is in the improvement and creation of new organisms that can be cultivated *in vitro* in many branches of substance conversion technologies.

From this author's standpoint, the term "biotechnology" can be understood as the complex of production processes that is based on the use of living organisms (microbes, yeasts, fungi, and the cells of higher eukaryotes) and bioactive substances isolated from living organisms (enzymes, antibodies, etc.) for the production of chemical substances and materials. The production processes are considered artificial ("reactor") processes, regardless of their content. In that sense, biotechnology can be called "production biotechnology" (PBT) whenever the product (a chemical substance or material) has value as a commodity and makes production profitable, even if the amount of the product is extremely small.

Below is an attempt to forecast the evolution of PBT in Estonia. Excluded from examination are classical PBT processes that are directly related to food production (fermentation processes) or agriculture. Nor are biological purification structures examined.

To date, Estonia has made definite achievements in the development of the theoretical bases of PBT. A good example is the participation of Tallin Technical University (then Tallin Polytechnic Institute) in the formulation of the theoretical bases and production techniques for the production and use of immobilized enzymes. That work served as the basis for the creation and implementation of the production of 6-aminopenicillanic acid (6-APA) via the use of immobilized penicillinamidase. The production process for 6-APA, which is an important intermediate in the manufacture of semisynthetic antibiotics, turned out to be extremely efficient in terms of production and economics, and in the early 1970s, it was instituted at Riga Medical Drug Plant, and then at the Saransk Medical Drug Plant. To date, the process has been used for the production of all the 6-APA in the USSR, and it produces a savings of millions of rubles every year. Alas, neither that process nor any other biocatalytic processes have been implemented in Estonia.

The biotechnology laboratory of the Tallin Technical University, in collaboration with other departments and organizations, has created unique biocatalytic bubble reactors to raise the efficiency of the action of immobilized enzymes and cells. The largest of those units, with a batch size of up to 40 kg of biocatalyst, has been successfully tested at the Vyru Dairy Products Combine. With immobilized β-galactosidase, more than a ton of glycoso-galactose syrup has been produced. A process involving hydrolysis of saccharose with immobilized cells is being prepared for introduction by the Tallin Technical University working in collaboration with the Institute of Microbiology of the Latvian Academy of Sciences.

At present, the biotechnology laboratory of Tallin Technical University is amplifying the work it is doing on the immobilization of metabolically active microbial cells, including cells used for the destruction of xenobiotics. A large laboratory unit for cryogel immobilization of cells has been developed and mastered.

To date, the only large-scale PBT process in Estonia is the production of fodder yeasts on sulfate liquor in a shop at the pulp and paper combine in Tallin. With an output of 5,000 tons per year, the shop is successful and is making a profit, despite a high level of amortization. It is supplying the amount of feed protein needed by agriculture and is reducing substantially the flow of waste water into the Gulf of Finland. However, in all probability, the production of cellulose in Tallin will be halted, which will mean that that shop will close. In terms of ecological considerations, the retooling of the shop for some other raw material is not justified. The production of fodder yeasts within the city is inadvisable: ensuring ecological safety would require purification structures that would be too expensive.

In addition, in Estonia there is no commercial production of typical large-tonnage PBT commodities (feed protein, amino acids, organic acids, enzymes, sugars, antibiotics and other medicines, etc.). That sets Estonia off unfavorably from the other two Baltic republics and, undoubtedly, is hindering the growth of large-tonnage PBT.

In a number of instances in Estonia, rather small-scale intrasector and intraeconomy PBT shops have been pioneered. Among them are shops for the growth of fodder yeasts on whey (Kuusalu), the production of chlorella biomass under artificial lighting (near Vykhma), the growth of amylolytic culture for the production of alcohol (Mayenear Tapa), multistage aerobic processing of swine manure to produce a microbial biomass (Adavere), and hydrolysis of peat to produce fodder yeasts (Kekhtna), to name a few. However, most of those shops were not economically profitable and were closed down, despite the completely satisfactory level of their equipment. For example, a rather large, advanced unit for the production of algae was dismantled. Production of β-cyclodextrin begun in Kuusalu after the output of high-quality experimental batches and scaling of the process was mothballed because of marketing difficulties.

Starters for ensilage are being produced in a few places. Continued development of methods for producing biological preparations for agriculture is being coordinated by the Center for Agrobiotechnology (in Tartu; director, Yu. Kumar). In that same center, production of veterinary vaccines continues.

Of the products of fine biotechnology, one should mention, first of all, prostanoids, whose synthesis from arachidonic acid is performed with a biocatalytic system of animal origin. That complex of operations is being developed by the Estonia Academy of Science Institute of Chemistry under the guidance of Academician Yu. Lille. Commercial synthesis of prostanoid preparations has been set up at an experimental plant at that institute. Despite the extremely small mass of the synthesized products, they have real commercial value.

Operations involving the production of monoclonal antibodies and their use in analytic systems (kits) are being conducted at a number of points, primarily at the Estonian Biocenter, at Tartu University (particularly at the university's Institute of General and Molecular Pathology), at the Kemoteks Enterprise at the Estonia Academy of Sciences Institute of Chemical and Biological Physics, and in the laboratory of applied biotechnology in the settlement of Pylva. All those operations are related to one another and could serve as the basis for creating commercial series production of analytic systems.

Closely related to biotechnology is also the production of polysaccharides from natural material. For a long time now, so-called estagar—a furcellarane-type gelling agent—has been produced on the island of Saaremaa (the settlement of Kyarla, near Kuressaare) from red algae. The industrial product is used in the confectionary industry. Methods for the production of agarose have been developed at Tartu University. That material, as well as its derivatives, is manufactured in the form of chemical reagents at the experimental plant of the Estonia Academy of Sciences Institute of Chemistry. The above-mentioned productions are stable and profitable.

A technology for the production of β-cyclodextrin has been developed at the Tallin Technical University. The production of a highly soluble carboxymethyl derivative of cyclodextrin may be viewed as a unique continuation of that work. In laboratory conditions, that substance is being manufactured as a custom reagent.

The further development of PBT in Estonia is being supported by the authors of the concept of the development of the chemical complex. The worldwide trends involving an increase in the role of PBT in the economy should also be adhered to in our country. Low material-intensity, the possibility of using recycled material, the absence of ecologically dangerous wastes, and the possibility of producing extremely valuable products make PBT extremely attractive to the economy of Estonia.

At present, however, when the economy is returning to market principles, PBT cannot be developed via some centrally created program. That is why the creation of large, specialized biotechnological enterprises or concerns is not called for in Estonia. The principal means of developing PBT will, in all probability, be the further development of low-capacity production units that will, on an entrepreneurial basis, coordinate their own operations with science and with other enterprises within the Soviet Union and abroad. The path to exportation will most probably be with that kind of specific, entrepreneurial approach. With the rapid development of PBT, the continual change in nomenclature, and the continual improvement of product quality on the world market, planning the nomenclature of production for the distant future is unthinkable.

However, in light of Estonia's need for separate PBT products and in light of the skill levels and interests of existing science groups, one can note several areas of development of PBT, which can be the following:

(1) production of starters and bacterial preparations for agriculture;

(2) production of medical, veterinary, and agrotechnical diagnostic test kits;

(3) production of medical and veterinary drugs and prophylactic agents;

(4) production of biochemical reagents and auxiliary materials, including slaughterhouse waste products;

(5) production of bioinsecticides;

(6) microbiological synthesis of vitamins in the form of feed additives;

(7) microbiological synthesis of industrial enzymes, particularly with the use of recombinant strains;

(8) isolation, biosynthesis, and modification of polysaccharides for production use.

The above list consists of guidelines. The specific aims and methods of any industry in the framework of those areas should be determined on the basis of business-industrial analysis and could largely be associated with

the establishment of industrial and commercial ties. The latter, in turn, is largely determined by chance. In light of the rather rapid change in the conditions on the world biotechnology market, the above list should not be considered exhaustive. It is entirely probable that some areas in the near future will encourage the most competition but cannot be precisely predicted today.

The issue of scientific-technical ties inside the Soviet Union merits special attention. Without discussing here the possible means of developing a state order, on which, of course, much in the development of technology and the economy depends, we should create the need for further maintaining and developing ties with the better science centers in the Soviet Union. In studies of problems associated with product marketing, it turns out that, in many cases, the Soviet Union alone is the most promising and, often, perhaps the only significant market. At the same time, we should not forget that many Western firms are interested primarily in Russia's market.

In that context, the development of production biotechnology in Estonia in the future should be associated with traditional ties with scientists of Moscow, Leningrad, and other science centers. In light of the special political situation of the Baltic republics and the level of development of production biotechnology in them, direct ties and cooperation among Lithuania, Latvia, and Estonia should play a much larger role. If those traditionally successful ties are to be further developed, there first needs to be a solid sharing of information. On the basis of that, joint research could be developed, ready-made technologies could be shared and improved upon, and joint ventures (particularly in the form of joint-stock companies) could be set up for production and marketing. The traditional method of drawing up coordination plans can hardly be successful for that. The solution of specific problems requires, first of all, the initiative of interested parties and agreement and mutually advantageous contracts on research, production, and product marketing.

Concerning Experience of Use of Industrial and Economic Potential of Enterprises in Public Health Care Development

917C0153 Moscow SOVETSKOYE ZDRAVOOKHRANENIYE in Russian No 10, Oct 90 pp 49-53

[Article by R. N. Kudryavtsev and S. I. Potapov; Medical and Sanitary Unit of Plant imeni V. A. Degtyarev, Kovrov]

UDC 614.2:331.483

[Abstract] Results obtained by the medical and sanitary unit of the V. A. Degtyarev plant in 1980-1989 showed the benefits derived from the involvement of the industrial and economic potential of large municipal enterprises in health care development. Implementation of a complex of social and economic, organizational and therapeutic and prophylactive measures permitted significant improvement of health care for the industrial workers, the city residents and the population of the region as a whole. Many problems of physicians and health workers were solved. Introduction of an integral program concerning the problem of intoxication and alcoholism reduced lost work time 3-fold and reduced morbidity and traumatism related to alcohol consumption significantly. Data concerning specific indicators of the medical and sanitary unit showed a significant decrease in morbidity with only a temporary loss of the capacity to work, in days of hospitalization per 100 persons, in mean length of hospitalization and in mortality. Reduction of loss of work time because of decrease of morbidity provided additional production of 17 million rubles in the 11th Five-Year Plan. Additional expenditures on health care were recouped quickly. Other enterprises may use this system to their benefit. References 11: Russian.

US Firm Donates Medicine to Moscow

917C0319A Moscow TRUD in Russian 1 Dec 90 p 1

[Article by V. Ramenskiy: "Medicine for the Capital"; first paragraph is source introduction]

[Text] Drugs worth $500,000 were sent as a gift to Muscovites by the American pharmaceutical firm Serle-Monsanto.

The drugs were cardiovascular, gastrointestinal, and antiinfection drugs. As announced, all the drugs will be distributed through district Moscow hospitals. We hope they will reach the individuals for whom they are intended, and not disappear without a trace, as has happened with so many other such gifts.

Providing drugs for the capital is not the only charitable deed done by Serle-Monsanto for the USSR. The Chicago Symphony Orchestra recently completed a successful tour in Moscow and Leningrad, and the firm was its sponsor.

Supreme Soviet Committee Reviews Pharmaceuticals Shortage

917C0349B Moscow IZVESTIYA in Russian No 8, 10 Jan 91 p 3

[Article by S. Tutorskaya: "There Aren't Any Tablets, and There Won't Be Any..."; first paragraph is source introduction]

[Text] The catastrophic situation with drugs was discussed at the joint meeting of the USSR Committee for People's Control and the USSR Supreme Soviet Committee for the Protection of Public Health.

At the meeting, I saw rather quickly that there aren't any pain-killers, and there won't be any. We don't have the most common of drugs that have always been in our pharmacies.

Physicians at the meeting said that soon we'll have to forget about treating people with chronic conditions. The drugs that we still have they are trying to send to the hospitals, where many of the patients come in serious condition. But that's where the catastrophe is about to happen. We must be ready, the USSR deputy minister of health, A. Baranov, said, for the time when every third individual with an illness will not be able to receive any drugs.

One can't say that nothing was done last year to provide drugs for those who need them. A great many drugs were dispatched to areas that had suffered natural and ecological disasters and to regions in which child and maternal mortality rates are high. The deputies raised this question: Hard currency was allocated by a resolution of the USSR Congress of People's Deputies for the acquisition abroad of needed drugs—just where are those drugs? The drugs are available, but for the most part, they're expensive.

In Kursk, for example, enterprises found the money to pay for part of the cost of medicines, and the hospitals were able to get them. But look, a week-long course of antibiotic treatment for a child can cost 117 rubles. And for drugs, the hospital receives 65 copecks per child per day—that's the norm. Even if not all the patients come in in serious condition, there's a constant danger of overspending. Since no one has helped the hospitals in a whole array of oblasts and republics, the drugs lie there alone (in the warehouses), and the patients are also alone (without any tablets). The hospitals don't carry what's expensive.

Of course, there's some leakage through dishonest people. At the Riga Market in Moscow, they told me, you can quietly buy the very same analgesic—10 rubles for a 30-copeck package. And you can also find any imported drug there, for any, so to speak, prescription.

Right now, many are tormented by this question: How did it come about that, for the most part, our production of drugs is unprofitable? There's not a single pharmaceutical firm abroad that would work in such conditions.

Soon there will be a rise in prices for the raw materials for drugs. And that means that nearly 1,200 drugs will be unprofitable for enterprises of the medical industry. And the work collectives of those enterprises will, right or wrong, refuse to manufacture them, which is what they're doing now.

Year after year, we were told over and over that we have inexpensive drugs. In the process, however, they forgot to add two important things. The first was that they were also paying very little for labor. The second was that our medical industry was so neglected that it wasn't capable of radically improving the quality of the drugs.

That's why, if you raise the issue today of the sharp rise in prices for drugs to thereby make them profitable, the following question immediately pops up: Is is morally right to take more from people for drugs that fail to meet not only world standards, but also the simplest specifications of technology and safety? The Tomsk Chemical and Pharmaceutical Plant in the year that just past sent pharmacies aspirin that in fact turned out to be strong antibiotic. And tablets of weak kafiol [as published] manufactured by the Baku Chemical and Pharmaceutical Plant contained foreign objects that turned out to be harmful insects. In all, over almost two years, enterprises of the medical and microbiological industry received nearly 500 complaints against its products. That's from the data provided by the Committee for People's Control. And as a memento, Skoryy [emergency medical service] physicians presented me with a gift of an ampule of diabazole. It's too bad the plant where it was manufactured isn't marked on it, because there's a piece of glass swimming around inside it. When you realize that nowadays, at the peak of the shortage, people often drink from ampules instead of taking tablets, well... Oh yes, you can get a good analgesic or validol (if it's available near you, and the inscription on the label is right).

This meeting, in spite of isolated attempts ran like former meetings, with people dressing others down and constantly swearing, was nevertheless quite unlike those before it. As hard as it was, people told the truth. There were not empty promises by the producers to "correct the situation within a month." The fact is that, in the West, the development of a new drug takes an investment of nearly $100 million. They adhere to extremely high product-quality standards. It's an entire system called "good production practice." For decades on end, they have been teaching, and coaching, and schooling personnel for the pharmaceutical industry. They invest a great deal in testing and packaging. And they don't scrimp on research or on finding new drugs.

However, our unquestionable poverty and the many years of out-and-out carelessness of our industry are not any kind of indulgence for our health-care and medical-industry organizers.

For many years now, because of incomplete medical statistics, there have been no sound, complete data on our country's drug needs. How many years now, in my memory alone, has there been talk of the automated management system, which is supposed to have stored all those data, as well as reports the availability of drugs for the various regions!

Furthermore, the specialists have long been saying that we have an enormous quantity of drugs that duplicate one another. In Brazil, they've reduced the number of drugs to 700; we have 3,000. Recently, an interdepartmental expert council defined 33 of the most important groups of drugs and suggested that 200 obsolete drugs be taken out of production. Who kept that work from being started and done a lot earlier?

More than once specialists have tried to tell us of the disastrous situation in the medical industry and of the absence of a mechanism for testing and introducing drugs. Things are especially bad in the preclinical stage of testing. Our scientists don't have good vivaria or pure lines of animals. Quite recently, there were plans for building, with foreign assistance, four plants where everything would be on a state-of-the-art level for both the drug quality and the drug testing process. But no funds at all have been allocated for those plants. How many articles did IZVESTIYA alone print about it—and for what? No one got the signals. As a result, we're making excellent drugs, but we can't manage to "be smart" about them or put them on the market.

And if our industry people want to pull production out of the quagmire, why, with everything collapsing, did they also take on the production of protein-vitamin concentrate? Why?

Those questions don't provide any consolation. It's understandable that if you slap people's hands, they lose their initiative. But it's also understandable that, when a new opportunity to work opens up, you need workers who haven't lost their initiative or their common sense.

And is there any common sense in the report that for 1991, no funds whatsoever have been allocated for the development of new drugs? Right now, nearly 50 scientific research institutes working in the pharmaceutical industry are in danger of closing.

If we are to begin manufacturing drugs on a par with the rest of the world, the entire pharmaceutical industry has to be re-equipped. We need to tax it favorably, not fleece it. To date, only the Moscow Oblast Executive Committee has adopted such a resolution: favorable taxation and state orders will enable it to survive but raw materials are so expensive and any and all contractual obligations are being violated. We need to maintain the level of scientific potential we have working for the industry. We need to find money—after all, we found it for cigarettes.

And if a number of plants that produce substances for drugs do not reopen in the future (they're often closed hastily, because someone thinks there's a danger where there actually isn't), there will be an honest-to-goodness crash with drugs—the hospitals won't have them, and

Skoryy won't either, and that will have a direct effect on the quality of our lives and on our lifespans.

The newspapers are already replete with advice from the arsenals of folk medicine. It's a good thing, what with the empty pharmacies. I can give some advice that's even more productive: don't get sick. Seriously, though, we need to save the dying pharmaceutical industry. The projects of the past, in which intelligent individuals decided that the CMEA countries would make drugs for us, have demonstrated their unsoundness. Not a single country in the world has decided it should abandon drug independence.

We need to save production lines that haven't been ruined yet, seeing to it at the same time that they are ecologically safe. With parochialism rearing its head again and ties of many years being broken, our business people need to "get into the action" more quickly. I wouldn't want to be in their shoes right now. Many of our krays and oblasts that have come to expect that someone else "must give them" drugs have themselves closed down the manufacture of raw materials.

And all the same, we must try to overcome the anarchy and—this is unavoidable—move to the level of the rest of the world's drug quality requirements. It will be hard, but we have to set that goal for ourselves. Otherwise, we won't be able to live any longer. Without high quality, there's no getting away from hesitating when it comes to selling our drugs abroad, apart from velvet antlers and medicinal herbs, where the cooperatives have taken the initiative.

The main thing is to rid ourselves of the false notion that there are the important industries (space! defense!) and the less important industries, where you can produce a grand effect without a sweat, with lesser efforts. No, the transition of the pharmaceutical industry to a modern track takes the best scientific minds, the best organizers, training for the personnel, and appropriate payment for their labor, without any kind of discount for poverty.

He is poor who allows himself to be poor.

Problems in Vaccine Production

917C0349C Moscow TRUD in Russian 6 Dec 90 p 2

[Article by V. Belitskiy: "Unprotected Against Disease...: That's the Fate of Millions of People, Because Vaccine Production, Not So Long Ago the Pride of Domestic Biotechnology, Is Paralyzed"]

[Text] Everything's astir at home...Everything is topsy-turvy. At work, on the trolley, in the Supreme Soviet, on the television, we can have a lively discussion for hours on end about whether, for example, deputy privileges should or shouldn't be taken away from a deputy who took part in the beating and robbery of a police colonel by a demonstrating crowd. It would seem that there's nothing to argue about—they show a film in which everything is clear, including what the deputy did. But no, the discussion goes on. As if it's democracy. The parties and the factions are reveling in the impressions they're making on the television viewers. At a time when the viewers would best be impressed by the efficacy of the law.

But just the opposite happened recently in Tashkent—something I would call a robbery of health, an attempt on the life not of one individual, but of millions. But it didn't bother the police, or television, or the parties and factions. Maybe it didn't bother them because such things aren't shown on television. If that's the case, then I want to suggest to Central Television a story for a small scandal.

The tragic culmination of the story is the shut-down of production of typhoid vaccine in Tashkent. The vaccine was being manufactured at the Vaktsina NPO [scientific production association], until the USSR Ministry of Health was forced to use its "veto" power as the result of a conclusion filed by the inspection services. What was the reason for the shut-down? The reason was one that's quite commonplace in our time: poor quality, lack of sterility, unstable composition. Think about it: drugs that aren't sterile, that is, they're contaminated. As the master of ceremonies says, the height of decline. Was it considered a scandal? Was there an investigation? Court? A prison term?

No, it was the same as with the police colonel—the law remained silent. And the Ministry of the Medical Industry, which has jurisdiction over the NPO, is, as they say, taking the matter under advisement: the ministry is trying to decide how to change production a little more cleverly so that it won't be closed again. I don't know exactly what product they intend to manufacture in that NPO now. How about nitrates, or toxic chemicals, or go straight to biological weapons? I only know that it shouldn't be allowed to manufacture drugs anymore.

Why not? Here's why. A year ago, at that same place, those same individuals were forced to close down production of tuberculosis vaccine for the very same reasons. For the uninitiated, that vaccine is given to children who are five or six days old. The question is asked, Could newborns be inoculated with an unsterile preparation? Does that need an answer? That's when I'd like to get the answer from the general director of the NPO, B. Vafakulov (his face on the television screen). The voice of the announcer offscreen would say at that moment that the Vaktsina NPO has manufactured 36 million of 54 million doses of the preparation needed by the country for inoculations. Opportunely, the Ministry of the Medical Industry promised the medical people that it would correct the situation by expanding the manufacture of the tuberculosis vaccine at the Stavropol plant. Inopportunely, certain circumstances prevented it from keeping those promises.

And at this point, it's time to move the story from the Tashkent NPO to its patron, the Ministry of the Medical

Industry. But not because nowadays the slogan "Pity not the patrons" is in vogue, but because that patron, forgive me, isn't worth pitying: it seems to be doing nothing. Decide for yourselves—can an honest-to-goodness, professional, responsible patron quietly do nothing when it's aware of the following figures—namely, that we have 500,000 tuberculosis patient in our country, and that every year, nearly 100,00 new cases are recorded, and around 20,000 die of the disease? I don't think a real, professional patron would stand idly by. And if the Ministry of the Medical Industry is doing nothing, then...you be the judge.

Meanwhile, it's too early to draw conclusions. We have to become acquainted with a second set in this pitiful story. At this point, I'd like to bring onto the television screen the deputy chief of the Main Epidemiological Administration of the USSR Ministry of Health, Gennadiy Onishchenko, who would familiarize us with the information elaborated above. And so, attention—here's Onishchenko's monologue:

"We recall, like a nightmare, the events of late 1988-early 1989, when, for five months, not a single dose of measles vaccine was manufactured by the only manufacturer in the country—the Moscow enterprise for the production of bacterial preparations, of that same Ministry of the Medical Industry. The reason is the same as before: the preparations weren't any good."

You should know that measles is a dangerous infection that results in various complications—encephalitis, convulsions, pneumonia—and often ends in death. Such complications occur in one out of every 10 cases of the illness. It has been estimated that if there were no inoculations, 63 million people would get the measles every year worldwide, and 1.3 million of them would die. For our country, those figures would be 1.7 million and 6,900, respectively.

At the same time, measles is a so-called controllable infection—a good vaccine makes it possible to deal with the infection and, moreover, to eliminate it completely. That's the same vaccine, please note, that the Moscow enterprise is supposed to be manufacturing and that it so shamefully and tragically failed to manufacture for five whole months.

The chain of failures in the production of the most important vaccines (keep in mind that vaccination is one of the most reliable means of preventing infections, and in a number of diseases, it's the only means) is no accident. Alas, it's the result of quite recent, "slightly improved", hasty actions. Indeed, until 1987, our country had produced an enormous achievement by comparison with other countries—a unique system for the production of immunobiological preparations, one that virtually satisfied all the needs of health care. All the enterprises and the control of them was located under one special central administration of the USSR Ministry of Health.

Let's, as the television people say, break into G. Onishchenko's monologue.

During the time he's talking about, there was a heated controversy in various parts of the country: it turned out that the favorite brainchild of Soviet biotechnology (not medical technology)—PVC, or protein-vitamin concentrate that is developed with special bacteria from petroleum paraffins—was extremely harmful for the Soviet people around that biological technology. Paprin, which is produced as a result of the production, is an extremely strong allergen. Releases of that protein into the air that resulted from flaws in the technology put thousands of people in hospital beds—the reader will easily recall the conflicts in Kirishi, Irkutsk, and other areas of elevated chemical hazard. And if you add to that the fact that feeding livestock paprin or other such synthetic substances is banned in civilized countries because of a whole list of harmful effects, then it becomes clear what a surprising reprimand it was for the Ministry of Medical and Microbiological Industry, part of which had been the until-then independent central administration of the Council of Ministers. Minister V. Bykov, who had experience working in the Central Committee of the CPSU, initially tried to solve the problem the way they did things there: silence the press. As I remember, in a phone call to our editorial office from Staraya Square they said we didn't need to write bad things about paprin, it would be better to put something together about its benefits.

And when the technology of "pressuring the press" didn't work, they tried, as I understand it, something from a different angle: they decided to "marry" the industrial production of feeds for animal husbandry, which was extremely profitable for the Ministry of the Medical Industry, to vaccines. But anyway, back to the words of Gennadiy Onishchenko:

"And so in 1987, the production of vaccines was transferred to the system of the Ministry of the Medical and Microbiological Industry. As we were assured then, the manufacture of vaccines would be the primary area involved in the development of biotechnology, and immunopreparations would be carried to unprecedented heights."

Just the opposite happened. The health care sector lost not only a number of vaccines, but also its confidence in the notion that those that were being manufactured would be of uniform quality. As it all turns out, those preparations were, for the ministry, secondary, accompanying product. Typically, today the Ministry of the Medical Industry is forced to use hard currency (from its own money, of course) to buy abroad immunobiological preparations for which there is a shortage. Nothing like that ever happened to us before in this country. Just the opposite—we used to sell vaccines! But this is how we're living today.

Well, now, it looks as if the story is nearing its end. The only things not clear are the answers to the classic questions for our country: Where are things better?

Who's at fault? What can be done? I don't think the first two questions are worth asking, because we'll just end up hearing truisms over and over again. But the third question is worth paying attention to. Here's how Onishchenko answers it:

"The republics that have announced their sovereignty obviously intend to take over the enterprises that used to be under Union jurisdiction. In general, I don't think we can get involved in that process. But as for enterprises that manufacture preparations used for the prevention of epidemics, we've all got to do some clear thinking together. The many years of experience involving the establishment of unique immunobiological production demonstrate that such production will not work properly without a standardized and, consequently, a centralized system of control and inspection, without a single methodology, or without a common (I'm not afraid of that unpopular word!) theoretical ideology."

On the other hand, the four years of experience in the destruction of vaccine production in the Ministry of the Medical Industry demonstrate no less clearly that that production can't remain there—the agency is too accustomed to making its money on feed for pigs to be able to quickly learn how to work for people. What can be done about it?

We think there needs to be created an independent concern or association that is not part of that ministry. Its founders, who would be interested not in commercial ends, but in the social ends of organization, would be, for example, the health ministries of the USSR and the republics, the Commission of the USSR Council of Ministers for Emergencies, the Committee for the Protection of Public Health of the Supreme Soviet of the country. Such a concern or association would absolutely have to be given a high priority even in today's extremely strained distribution of finances, plus a preferential line of credit. That problem is just as urgent as the problem of drugs.

If the television program on vaccines were actually broadcast, at that point I would have some sort of especially meaningful pause and I would remind the viewer that all the moaning about the lack of drugs and the collapse of their production at the enterprises of that same Ministry of the Medical Industry has been going on for years. Even a child knows that very soon the shortage of drugs will reach catastrophic levels everywhere. But it's typical that, according to certain data, the Ministry of the Medical Industry is contriving, as it were, to remain one of the most systematically successful agencies (what are they capitalizing on—surely not on the denounced protein-vitamin concentrate?). On the other hand, no decisive actions of any kind on the part of either the executive or the legislative authorities have been taken. It's as if the authorities are accustomed to waiting until the situation is no longer explosive. But can it really be that no one on the "top floor" understands that the next issue they'll have to deal with will be labelled "emergency measures to rectify the tragic situation caused by the total lack of drugs"?

It's that very issue I'd like to submit for study in the USSR Supreme Soviet in place of some other issue that's been placed on the agenda. Or even in addition to those that are on the agenda. Against the backdrop of that issue, I don't think a discussion about the rights of this or that deputy or about, say, a law ensuring the execution of other laws would last very long.

Kazakh Health Minister Interview

917C0354A Moscow RABOCHAYA TRIBUNA in Russian 12 Dec 90 p 1

[Interview of Aksultan Amanbayevich Amanbayev, KaSSR health minister, by MEDITSINSKAYA GAZETA special correspondent Sergey Shilov, under the rubric "Your Opinion, Mr. Minister?": "Aksultan Amanbayev: Not Waiting for Favors From the State Budget"; first two paragraphs are source introduction]

[Text] If it's true that 50 is the "most ministerial" age, then A. A. Amanbayev was named minister of health of the KaSSR just in time—a week before his fiftieth birthday, in April of last year. Before that, he had studied in the therapy department of the Alma-Ata Medical Institute, had worked seven years as a surgeon and as deputy chief physician in the rayon hospital in the Chimkent Oblast. After that, he went back to school: he did a clinical residency and was in postgraduate studies at the Scientific Research Institute of Clinical and Experimental Surgery imeni A. N. Syzganov. Then he spent seven years as senior research associate and surgeon in the department of cardiovascular surgery of that same institute. In 1984-1987, A. A. Amanbayev served as deputy head of the Department for Education and Health Care of the KaSSR Council of Ministers Administration of Business Affairs, and in 1987, he was named deputy minister and chief of the IV Main Administration of the republic's health ministry.

Today, KaSSR Minister of Health A. A. Amanbayev answers the MEDITSINSKAYA GAZETA correspondent's questions.

Shilov: Aksultan Amanbayevich, Kazakhstan health care is known to have a great many problems. But what in particular concerns you the most, as health minister?

Amanbayev: The problems are, in fact, many. And the difficulties associated with the solution of some are due to the unresolvability of others. The level of infectious morbidity is high, especially in the southern oblasts of the republic. The reasons for that are poor diagnostics, unsatisfactory hygiene conditions in many population centers, and, of course, the weak material-and-technical base of most of the medical facilities. Today, for every resident of the republic, there are a total of 84 rubles from the fixed capital of the health care system. That's a tenth of what the specialists recommend!

In recent years, the state of health of rural residents has tended to get worse, and the number of individuals with oncological, allergic, and cardiovascular diseases has grown, as has the number with congenital anomalies, sugar diabetes, tuberculosis, and brucellosis. And again, I must mention the material-and-technical base. Of the 5,218 rural paramedic-obstetrics stations in the republic, only 220 are located in standard buildings, and 198 occupy emergency accommodations.

The ecological situation needs special attention. In eastern Kazakhstan, the air is polluted with lead, and the ground water is polluted with the salts of heavy metals. The Chimkent and Dzhambul oblasts continue to have the problem of phosphorus intoxication. The air and the ground water of Aktyubinsk Oblast have an excess of fluorine. As before, petroleum refining in Guryev Oblast is polluting the environment. And I'm not even talking about the Aral Sea region.

Shilov: Could you give us a little more detail about that particular region?

Amanbayev: The Aral Sea region right now is practically unsuitable for normal living. Thousands of Aral Sea residents are abandoning their birthplaces. And those who remain have the most varied of diseases, especially acute infections. We went to the republic's Gosplan with a proposal to build, in the next five years, nine hospitals with a total of 2,000 beds, seven polyclinics to handle 2,250 visits per shift, a somatic sanatorium to handle 150 people, seven rayon pharmacies and 20 rural pharmacies, three rayon sanitation-epidemiological stations, and a dairy kitchen. In the Aral Sea region at the moment, a comprehensive study of the state of health of the population is under way, and a list is being made of the medical equipment that will be issued to that region above the republic's allocations. The activity of many scientific research institutes and higher education institutions is geared to solving the problems of the Aral Sea region.

Shilov: And what can you say about the situation in Semipalatinsk?

Amanbayev: We have no doubt whatsoever that the health of the population living near the nuclear testing grounds is suffering ill effects (that area, by the way, also includes certain rayons of the Pavlodar and Karaganda oblasts). We are faced with the task of ascertaining the extent of those effects, of making forecasts for the coming decades, and, based on those forecasts, of developing a program for rehabilitation. Forty teams of experienced scientists and medical people are handling that task right now. Above-allocation medications and medical equipment are being sent to Semipalatinsk, and seven health care facilities will be built there in the coming years: hospitals with a total of 2,000 beds, and polyclinics to handle 1,700 visits per shift.

Shilov: Aksultan Amanbayevich, all that requires enormous expense. But the market is approaching, and building materials are becoming more expensive, as are drugs and medical equipment...

Amanbayev: Yes, that's how it'll be very soon. That's why we plan to ask the Supreme Soviet of the republic and the Council of Ministers to increase the appropriations for health care. But that doesn't mean that we're, as they say, waiting for any favors from the one who puts the state budget together. No, we ourselves are preparing for operation in the new conditions. Right now, in five regions of the republic, an experiment is under way to introduce the new economic mechanism into the health care system. Recently at the board of the ministry, we discussed the results of the experiment and reached the conclusion that the mechanism needs to be gradually introduced throughout the entire republic. We are developing collective forms of labor organization and leasing ties. Last year, the number of economic agreements with industrial enterprises and other enterprises regarding the provision of above-norm medical care rose sharply. Day hospitals and night hospitals are being created, as are centers for outpatient surgical care. That will make it possible to use the funds allocated to the sector more efficiently. Insured medicine should also be an additional source of financing.

Shilov: And how do you feel about fee-based medicine and the medical cooperatives?

Amanbayev: I am for the coexistence of all kinds of medical care provision, but on the condition that state-guaranteed free treatment enjoys complete sufficiency. That, I feel, is a crucial achievement of socialism. I am against the idea of turning the treatment of poor people (they are the very ones who need medical care most often) into a source of revenue for those who deal in medicine. As for paid services, we plan to increase their volume by 1996 by more than twofold and bring it to 126.6 million rubles. Especially since the rendering of medical care for money disciplines the physician and forces him to apply a maximum of effort in healing the patient.

Shilov: Speaking of physicians, I'd like to address one other "sore spot" of Kazakhstan health care—the low skill levels of many medical people...

Amanbayev: Unfortunately, that's the case. About two years ago, tuberculosis specialists were being certified in Guryev Oblast. It turned out that the level of training of one out of three physicians of that specialty didn't meet the requirements. And that in the worst oblast for tuberculosis! The level of knowledge of many of our medical institute graduates is clearly inadequate. Of course, that's not true of all of them. The Karaganda and Tselinograd institutes, for example, can hold a candle to the best higher education institutions in the country in just about regard. And yet, in that same Karaganda Medical Institute, a total of 1,578 rubles are spent annually for the training of each student—a figure that's an order of magnitude less than the figure abroad. Today in the republic, there are 4.2 sq. meters of study space per

medical student. The dormitories can accommodate 79 percent of the students. There should be one instructor for every five students—but in our higher educations institutions, there's one for every eight or nine. I think you'd agree that all that doesn't help to graduate good specialists.

How do we intend to change the situation? First of all, we are going to curtail admissions to the first years of study in the medical institutes considerably. Our annual needs in terms of medical personnel in the republic consist of roughly 1,050 physicians and 5,500 mid-level medical workers. Every year, we graduate nearly 3,000 physicians and more than 10,000 doctor's assistants and nurses. That cutback, combined with the construction of new educational buildings, will make it possible to match up the student contingent and the material-and-technical bases of the higher educations institutions. In addition, we've decided to make the requirements for taking admission exams tougher, implement a permanent system of quality control in the training of specialists, and introduce state exams in such basic disciplines as normal anatomy and physiology, histology, and biochemistry. So that a careless or incompetent individual will have very little chance of receiving a physician's degree.

Shilov: These days, we're always hearing about the shortage of medical personnel, and you want to cut back on admissions?

Amanbayev: That primarily pertains to remote areas. If, for example, the number of medical personnel in the cities is 80 per 10,000 population, that figure is roughly 27 in the Chimkent and Dzhambul oblasts. That is, we're faced with the problem of assigning medical personnel to the village. I think the local soviets, enterprises, sovkhozes and the kolkhozes could help us out in that regard by paying the difference for the medical personnel who work in their regions. Another reason for the turnover of medical personnel is the unavailability of housing. But I feel certain that the same local soviets could solve that problem, too. Why couldn't they adopt a resolution to allot medical personnel, say, 10 percent of the housing that's rented out for use? Or set up for medical workers the same kind of procedures for getting a loan for individual housing construction that has been set up, for example, for kolkhoz workers? Yet another means of solving the housing problems for medical workers is to approve only integrated designs for treatment-and-prevention facilities. You're building a hospital? Well, then be so kind as to also build homes for the medical personnel who are going to work in that hospital. And look how many female medical personnel are forced to stay at home with young children! The local soviets could also provide space for their children in preschool facilities. To do that takes only one thing: the understanding that all those measures will, in the final analysis, work to the benefit of thousands and thousands of our patients.

Shilov: Aksultan Amanbayevich, the medical people often complain of the shortage of hospital beds...

Amanbayev: We are taking measures that will enable us to use the bed fund more efficiently and to shorten hospital stays. By 1995, we plan to have opened 14 diagnostic centers in Kazakhstan. The first of them opened two years ago, in the capital of the republic, and two more will open in the next few months, in Karaganda and in Chimkent. In light of the demographics of Kazakhstan, we feel it necessary to develop a network of nursing care homes, shelters, and boarding houses for elderly, chronically ill patients.

Shilov: Recently, the KaSSR Supreme Soviet adopted declaration of state sovereignty for the republic. How do you think that event will affect the state of affairs in Kazakhstan health care?

Amanbayev: With sovereignty, of course, we'll be able to solve more quickly certain problems that stand before us. That pertains primarily to financing, the revision of certain norms to suit our needs, the restriction of the arbitrary rule of agencies that are polluters of the environment. But sovereignty will in no way weaken our ties with the Union ministry of health or with the ministries of the other republics. We have, for example, very close ties with the medical and scientific institutions of the republics of Central Asia, with whom we are cooperating in the area of environmental protection in border regions and in the treatment of territorial diseases. We intend to work together with the medical people of Russia, the Ukraine, and Belorussia in preventing the ill effects of ionizing radiation and in solving other problems, primarily those of a fundamental nature.

Shilov: And finally, one last, not quite ordinary question: Is it hard being a minister?

Amanbayev: That is, in fact, an unusual question. I've never even raised that question to myself, never even thought about it. Being a minister is a responsibility. You have to justify the trust that's placed in you.

Food Shortages Affect Health of Diabetics

917C0354C Moscow VECHERNYAYA MOSKVA in Russian 15 Jan 91 p 1

[Article by Marika Toomingas: "The Shortage for Diabetics"]

[Text] With the epidemic shortages, diabetes mellitus patients may have their own store, but they are experiencing big difficulties. Several letters have come to the editor about that. The reason for the letters was the remark of Enn Rebas concerning the fact that he was refused four loaves of diabetic bread.

Reader A. F. replies: "In their passports, diabetics have the recommendation of the endocrinologist, which indicates that the diabetic can eat 150 grams of black bread a day. If they give you four loaves, then some other

patient won't get his 150 grams." The author of that letter doesn't agree with the regulation that says that diabetes mellitus patients who receive insulin injections are served ahead of everyone else. Here's her argument: they go wherever and whenever they please to make all kinds of purchases, but for dietetic products, for some reason, they can't stand a while in line...

The diabetics are often themselves at fault for the long lines in the diabetic stores and for the fact that there aren't enough products to go around. That opinion was expressed and supported by many readers. "For meat products," writes reader Daniel, "people stand in line for entire days, and maybe the same ones. Who is unable to stand? Here's a suggestion: we need to make it so that every patient at least once a month is guaranteed to receive a certain amount of by-products. For recording it in the patient's passport, a mark needs to be made like one for groats."

Diabetics doubt that everyone standing in line receives the products specified in their personal paperwork. However, A. F. feels that the sellers shouldn't be blamed. To bring some order to the matter, products should be issued on the basis of other documents, not on the basis of a note from the doctor about the patient needing additional help; that practice should be forbidden. The best thing of all to do would be to compile a list, because otherwise several people will be coming in with notes for one and the same diabetic. There are a lot of diabetics, but those who need additional help are few.

"I'm not a diabetic, but I've been a group II invalid for 24 years," writes Stepchenko. "And I also need a special diet. And how can I maintain it, if coupons can't always be issued? I don't have the strength to go looking for the products I need, I don't have my health. So I'm shocked at how diabetics, after using their paperwork to get vegetable oil, and buckwheat, and sausage, can in conscience speculate with them (buckwheat—3-4 rubles a kilo, oil—4 rubles a bottle). I can't even remember when was the last time I saw those things for sale."

Other readers also report of diabetics supplying their relatives and friends with products bought in diabetic stores. With that kind of a situation, it's hard to feel that everybody is suffering a shortage.

We think that for all the complexity of the situation, the workers in those stores should listen to the readers' advice. Maybe then something could be changed in the distribution system that's come about.

Hard Currency Obstacle to Insulin Program

917C0354D Moscow VECHERNYAYA MOSKVA in Russian 21 Dec 90 p 1

[Article by V. Kucherenko, under the rubric "Perestroyka: Quality of Health Care": "Hard Currency 'Famine' and the 'Insulin' Program"; first paragraph is source introduction]

[Text] Today, in our country, nearly a million people suffer from the most severe form of diabetes mellitus—insulin-dependent diabetes. Some 26,000 of them are Muscovites. In order to live, those individuals must receive an insulin injection every day for the rest of their lives.

Almost all the letters we received from the readers of our column express alarm about the interruption in the supply of those medications. Data from a sociological study conducted by "Antidiabet" [Antidiabetes] portray a depressing picture of the situation in which Moscow diabetics find themselves.

Today, there is an emergency situation with regard to the supply of high-quality insulin preparations. Production of obsolete insulins that cause complications has been halted at the plants of the USSR Ministry of the Medical Industry, which means that the lives of the diabetics depend on the government hard-currency appropriations for the import of those critical drugs. But there aren't any solid guarantees, even though the Soviet Union is a signatory of a convention that obliges the financing of measures geared to preserving and extending the lives of diabetics.

Yes, at the 1st Congress of People's Deputies of the USSR, the head of the government promised to purchase a "running" plant for the production of insulin preparations at a cost of 200-300 million in hard currency. However, the hard-curreny "famine" that has broken out is burying that plan, and the import and timely delivery of preparations to the country may be disrupted. And that means that diabetics find themselves hostages to our hard-currency insolvency.

The time has come for city officials to pay very close attention to the diabetes problem. They need to immediately form a city "Diabetes Mellitus" program and recruit specialists and all interested individuals. One of its most important points must be to become a part of the "Insulin" program. We support the chairman of the permanent commission of the Moscow council for protection of public health, L. Kolosov, and the chief of the city's Main Medical Administration, R. Anufriyev, in that Moscow needs its own drug industry, one that includes drugs for diabetics. We can create joint-stock enterprises and joint ventures with foreign firms, and we can develop for implementation a program of operations involving natural and genetically engineered domestic insulins. All that takes about 30 million rubles.

But will the city be able to set up production of these vitally necessary medications?

"The task is entirely feasible," says A. S. Novokhatskiy, doctor of medical sciences and deputy director of the All-Union Scientific Research Institute of Blood Substitutes and Hormonal Preparations. "We have formulated a state-of-the-art concept for the production of domestic insulin, and we have developed the requirements for kits and drug quality. The preparation of the technology for the manufacture of seven substances and 20 medicinal

forms of animal insulin that meet world standards is drawing near an end. After all, the search for preparation forms is taking the same route here and in the West. The tempo of experimental-industrial testing is picking up. In June, the Pharmaceutical Committee of the USSR Ministry of Health allowed clinical tests of the first domestic single-component preparations—monosu-insulin MK and insulin-semilong MK."

But this coming year [1991], execution of the state program of operations for domestic insulins may be on the threshold of collapse. Beginning 1 January, the financing of the research on the insulins will actually be closed down. To continue that research, the institute needs 4 million simple, nonconvertible rubles. The USSR Ministry of the Medical Industry doesn't have any money, because in the transition to the new economic conditions, it lost centralized funds, and the plants of the sector can't "pick up" such a large sum.

"What are we supposed to do?" argues Novokhatskiy. "The institute, of course, will survive. We can conclude, say, economic agreements involving the development of methods for purifying waste water or for processing the wastes of meat combines. But the vitally important program for insulins will die, and the strong creative groups will disintegrate. If we hadn't lagged behind the West earlier in the laboratory, then right now we could lose that, too. Incidentally, the Institute of Antibiotics is in the same fix, with no place to get 3 million rubles to continue work on genetically engineered insulin..."

And so the Union government is practically wrapping up the "Insulin" program. Is it worth it for the city to finance its own? Let's see. In the first place, we would rescue diabetic Muscovites from the unenviable lot of being hostage to those who are in charge of the hard currency. Second, the capital could realize a little of its "brain" potential and crank up for itself a production that wouldn't require a lot of resources and would be modern and science-intensive. The eyes of all the diabetics in the country would again turn to Moscow, and mutually beneficial commerce with other regions would be set up.

In general, the city officials have something to think about. And this matter can't be put on the back burner.

Chernobyl Cleanup Participant on Health Effect

917C0422A Riga SOVETSKAYA MOLODEZH in Russian 27 Feb 91 p 4

[Article by Dmitriy Mart, under the rubric "Contemporary Monologues": "The Only Thing That Should Not Be Borrowed From People Is Pain and Endurance"]

UDC 577.13+611.018.5

[Text] I overheard a conversation on a trolley bus, and then invited myself to the home of one of the interlocutors for a chat. Vyacheslav Mikhaylovich Yashin, a driver for the Second Automotive Combine, repeatedly underscored his request that I report his words exactly as they came out of his mouth, without abridgements or distortions. Nevertheless, I decided to omit the harshest expressions.

"I participated for three months in the elimination of the consequences of the accident at the Chernobyl NPP," Vyacheslav Mikhaylovich began to recount, "up till November 1986. At first I couldn't get in because of my age. I was 45 years old. But call-ups kept coming out of the military commissariat, there were eight of them. So although my age wouldn't permit, they took me anyway. Commissar Kostin of the Moscow District Military Commissariat ordered us to write a declaration that we were going voluntarily. Then they loaded us on a "Boeing" (that's what we called our military assault landing craft) and sent us there. Our regiment, the Riga, as we called it, set up camp at Budovitsy, 56 km from Chernobyl, in a swampy area, in the "nuclear-free zone", as we joked grimly at that time. They lied to us, that there was no radiation there.

"What were we doing? At first, in essence, foolishness: we removed contaminated earth by hand with shovels, which we then loaded onto trucks. We worked 16 hours a day, except for Saturdays and Sundays. At that time no one yet knew how contaminated the earth was. We worked in a standard military uniform: boots, military blouse. We lived in tents. We lived like dogs! There wasn't even water. We didn't wash for months. They just brought in water for cooking. We couldn't even launder our underwear or outer clothes. Estonian and Stavropol regiments were next to us. They had the same situation.

"Why do I say that what we were doing was foolishness? Because moving earth with a shovel is the same thing as carrying water in a sieve. Today we clean up here. Tomorrow the reactor spits here again. Again we clean it up. But try to say anything to the bosses! The commander of our battalion said, almost swearing: 'You'll end up court-martialled! Shut up!' For sure, they treat dogs better than us.

"Just the other day they buried a 49-year-old guy from the Riga regiment. A very young guy.

"We worked, we did nothing but work. They didn't think of us as people, and we lived like cattle. If you only knew what the hell was going on there! What lawlessness, what thievery! How terrible it was there!

"The trucks with stuff from the towns were checked by the cops, the lowest of the low, who condemned as defective whatever caught their eye, which they set aside in a special drawer to take away for later sale. From the burial grounds, where everything was dumped together, they plundered anything of the slightest value. They also dumped vehicles of all different trademarks, which the militia workers traded right and left. Do you need a power unit, a motor, any old part- just ask! If it's the whole machine, they break off the numbers. The mafia ran the whole show, and then they compacted the rest with tanks.

"When you went through the dead zone, it was awful. All the wells were sealed up. Not a living thing, but man was there. On the way back we picked up a bottle or two of mineral water, that was all the water there was. A cruel time, inhuman!

"Then, on September 6, our regiment was the first to go to the reactor floor, 'into the stack', as they said. We only went in September, because in the summer they didn't know what to do. They waited for the Americans and the Japanese, who explained what had to be done. Hammer came from the US.

"They formed us into battalions. Our commander, who was never sober, began in a drunken voice: 'Whoever wants to! Whoever wants a pile of medals and a pile of money, step forward!' I stood behind everyone, as the oldest, and the youngest ones were in front, kids, like you. At that point I stepped forward, and then they said to me, 'Hey, old man, where are you going?' Turning around I answered them: 'Today I'm falling out on my own, guys, tomorrow they'll be sending the rest of you whether you like it or not!' Yeah, and they did send them all... to die.

"They handed out a spacesuit and protective clothing for the work. In general, a private got 500 rubles for 25 roentgens, an extended-service regular got 1000 rubles, but the servicemen were not lured even by this money. We also refused, even though they promised us five times as much. Then, remembering that we were subject to the order of the USSR Minister of Defense, they ordered us, and we took the oath. So they drove us, cannon fodder, there. We went in twos. The work was a minute and half on the floor, plus as much extra time as we needed on the ladder on the stack in order to get to it. They brought us over to the TV screen: 'You see that gismo over there? Get it off the reactor floor.' Forward march! The reactor kept spitting up all kinds of crap on the floor. When the first ones went in, they stuck Japanese dosimeters on their chests, under the lead jacket, and then they saw themselves how many roentgens they were accumulating ... 24, 28, 35, 40, and all this for a minute and half on the floor. And the peacetime norm for a military man is 25 roentgens. So a decree came out: don't look at the dosimeters yourselves. This was entrusted to the representatives of the authorities, and they, of course, began to lie: 'You have 5 roentgens... You have 6... .' So on the whole, as usual, they acted dishonestly.

"There were those who wrote their buddies up for extra roentgens, so they would beat it out of the station a little bit faster. I know how they promoted a major to a lieutenant-colonel for 'self-sacrificing work'.

"There was also some window dressing going on somewhere. The half-marasmic Shcherbitskiy came. They put on some concerts somewhere. They say that even Alla Pugacheva came. But, except for work, we saw nothing.

"And what they fed us! The most contaminated meat of just slaughtered cows. They fed us large chunks of that. You know the care the party and the government takes of the working people, that's what they say. But all around us was just the dead zone, and the work was 16 hours a day. Vodka? There was no vodka. Only the Ukrainians ran a still and sold three liter jars for 70-80 rubles apiece. After your shift you drink 100 grams, and whoever has a half-liter bottle, drinks it... and to bed until morning. There were suicides too. People hanged themselves. One guy hanged himself near the commander's tent on the day we got there. Then the doctor I flew there with hanged himself in the swamp. And nobody says why...

"There was a young kid with me, we went in the steam to the reactor floor. We both did the same work. But in the morning he didn't get up. They took him to Kiev. Is he still alive?

"I still went on working after that: I washed the radiation off the machines and trucked concrete over to the station. So I don't know exactly how many roentgens I accumulated. They paid us, it makes me laugh to say it, three rubles in traveling expenses a day.

"When I returned I began to feel worse and worse. It was bad, very bad! At the Popov Plant, where I was working at that time, they gave me a vacation pass for Pyatigorsk. And that's all. I was completely forgotten. God, where's the fairness in that!? I went to the military unit at Yauntsiems, where they had formed our Riga regiment, but the commander just sent me on. At the plant's bookkeeping office they said: 'We don't know anything about where you were! All your papers are useless scraps. And the kind of paper you have you can get at any local military unit... ' So you couldn't get the truth there either. In 'civilian life' they haven't acknowledged us! So who's going to settle with us? At the republic's Latvian Republican Trade Union Council [LRSPS] they said that they will pay without taking the work on days off into account. It was possible to get it only through court, and a paper came from the Ministry of Defense for them to pay us for Saturdays and Sundays. But they still haven't paid us for the 16 hour days. They say that '16 hour work days are not provided for in Soviet law'.

"But then, at that time, before we were sent, what didn't they promise us! But so far, nothing! The Secretaries of the Moscow District sang like nightingales: 'In the name of peace, progress, in the name of this, that, and the other... ' Where is their conscience? 'Look, the whole world is watching you! We will shower you with benefits!' And they sent us off. And now my only benefit is to spit in their faces!

"I went to the Military Commissariat, and they said to me: 'What do you need from us? What is this truth you're looking for? We have Afghanistan vets with their arms and legs torn off, and you're pushing your way in!... ' And then they say: 'What's the matter with you, couldn't you buy your way out?' And how was I supposed to buy my way out? I didn't know when, to whom, and how much I had to give so they wouldn't send me. And anyway, I didn't think they'd send me beause of my age.

A month and a half after the sanatorium I couldn't get around any more at all. Everything hurt. But I managed to find an old lady from Tukums who fixed me up a little with salves. A thousand and a half went for that.

"And if I go to the polyclinic, the doctor says to me: 'You have a chondrosis! You have an allergy!' etc. But where did this chondrosis, this allergy come from; after all, I had been a healthy fellow! And as for medicines 'there's none, none, none'.

"At the Council of Ministers polyclinic they answered: 'Who shipped you over here? We have no medicines!' Is it possible they can't even give an injection? So where else am I supposed to go? So I spit on them all..."

"But isn't there a Latvian 'Chernobyl' union?"

"Sure, I paid 15 rubles to the bank on Ludzas Street to join and for a diploma, so now what? They said that they will register me at the order department, and at the store for the disabled. I was about to apply there, but they said to me: 'Shut your book! We know how you worked there!'

"Families are falling apart: men who spent time there are often no longer able to handle family life. And who's going to pay the mothers, the wives, the families of those who have perished, who have died?"

Dmitriy Mart

P. S. It will soon be five years that the tragedy happened. I well remember the panic of that year. I was serving in the army myself at that time, but only in Moscow. The troops marched along the unit's square with flag-waving patriotic songs. The rains came at the end of April and the beginning of May. Then, when the "enemy voices" reported that the death-dealing cloud had swept over Moscow too, and that the children in the districts surrounding Chernobyl were becoming ill, our Ukrainians and Belorussians began to long for home. But no one let them go. The pregnant wife of my friend, the unit artist, Yuriy Sarnavskiy, came to him; she had been evacuated from Gomel ("Go wherever you wish!"). So she lived at the unit's regimental command post [KPP] until they set her up somewhere. Our own newspapers calmed us down. It's nothing terrible, see how reliably the helicopters have been covered with lead sheets, how splendid is the regalia of the people who are saving us and you...

Health Ministry Warns Against Black-Market Pharmaceuticals

917C0423A Riga MOLODEZH ESTONII in Russian 8 Feb 91 p 1

[Question by L. Voyevodina and answer by Maye Tambik: "Hello, We Hear You!"]

[Text] Recently, I have encountered the following warnings in newspapers several times: Buy all drugs only in pharmacies. With what is this connected?

L. Voyevodina: With nothing else, but the shortage and its derivatives—we decided and, on the whole, proved to be right.

"It is primarily a matter of guaranteeing the quality of medicinal preparations," Maye Tambik, deputy general director of the Estfarmatsiya Association, explained. "Up to now the republic has received almost all drugs in a centralized manner, through all-Union channels. First of all, they undergo a check in the Central Analytic Control Laboratory, after which they arrive in pharmacies, which are responsible for the correspondence of drugs to standard requirements. Point 5 of the Decree No 245 dated 26 November 1990 of the Government of the Estonian Republic—Rules of Registration and Sale of Medicinal Substances and Preparations—establishes that only wholesale enterprises or pharmacies, which have state licenses, can engage in trading them. The Ministry of Health of the Estonian Republic issues them.

"Recently, people have been increasingly trading from hand to hand at speculative prices (for the 5-ruble antirheumatic agent "rumalon" they ask 100 and more—even foreign currency). They sometimes sell obtained things in whole batches. And no one will give you guarantees that the original preparation, without additives or substitutes, is in the package. This also applies to disposable syringes, which appear in cooperative kiosks. They can simply turn out to be stolen from a hospital, as was the case, for example, in Tartu, or, what is even worse, not sterile. Possibly, private pharmacists and whole pharmacies will appear in the republic in the near future. I am for this, but on legal grounds and with reliable control."

Disease Statistics

917C0460 Moscow VESTNIK STATISTIKI in Russian No 12, Jan 91 pp 48-51

[Nine tables taken from VESTNIK STATISTIKI, under the head "Morbidity Rates Among the Population"]

[Text]

Morbidity rates for alcoholism and drug abuse

	1980	1985	1986	1987	1988	1989
Individuals newly diagnosed with						
alcoholism or alcoholic psychosis						
in thousands	545.7	601.3	548.0	510.8	439.1	426.5
per 100,000 population	205.8	216.9	195.8	180.7	153.8	148.9
drug abuse or toxic-substance abuse						

Morbidity rates for alcoholism and drug abuse (Continued)

	1980	1985	1986	1987	1988	1989
in thousands	3.6	9.6	16.4	24.3	17.1	15.4
per 100,000 population	1.3	3.5	5.8	8.6	6.0	5.4
Individuals registered at treatment-and-prevention facilities (at year's end) with a diagnosis of						
alcoholism or alcoholic psychosis						
in thousands	3289	4491	4551	4625	4580	4297
per 100,000 population	1235	1613	1618	1628	1598	1495
drug abuse or toxic-substance abuse						
in thousands	36.2	41.5	47.9	61.1	69.5	73.4
per 100,000 population	13.6	14.9	17.1	21.5	24.3	25.5

Morbidity rates for venereal disease

	1980	1985	1986	1987	1988	1989
Individuals newly diagnosed with						
syphilis						
in thousands	52.4	26.8	21.1	16.0	12.6	11.9
per 100,000 population	19.7	9.7	7.6	5.6	4.4	4.1
gonorrhea						
in thousands	392.6	313.1	264.8	243.9	258.9	302.9
per 100,000 population	148.0	113.0	94.6	86.3	90.7	105.7
Individuals with syphilis registered at treatment-and-prevention facilities						
in thousands	313.1	210.7	181.9	152.2	125.3	103.9
per 100,000 population	117.6	75.6	64.7	53.6	43.7	36.2

Individuals newly diagnosed with veneral disease in 1989, by sex and age

	Syphilis, in thousands		Gonorrhea, in thousands		Per 100,000 individuals of same age			
					Syphilis		Gonorrhea	
Age, in years	Male	Female	Male	Female	Male	Female	Male	Female
All ages	6.4	5.5	168.6	134.3	4.7	3.6	124.7	88.7
0-14	0.03	0.04	0.2	2.2	0.1	0.1	0.5	6.0
15-17	0.2	0.3	10.8	14.8	2.3	4.9	162.6	229.1
18-19	0.2	0.6	26.6	23.4	5.5	13.8	385.1	579.4
20-29	2.9	2.5	106.4	66.5	12.9	11.3	477.3	302.3
30-39	1.9	1.3	26.3	19.7	8.4	5.7	118.5	87.7
40 or older	1.2	0.8	8.3	7.7	2.9	1.3	19.7	12.9

Morbidity rates for active tuberculosis

	1980	1985	1986	1987	1988	1989
Individuals newly diagnosed						
in thousands	133.1	126.8	125.4	123.7	119.8	114.5
per 100,000 population	50.2	45.7	44.8	43.7	42.0	40.0
Those with active tuberculosis of the respiratory ogans						

Morbidity rates for active tuberculosis (Continued)

	1980	1985	1986	1987	1988	1989
in thousands	116.1	113.7	112.4	111.1	107.5	102.9
per 100,000 population	43.7	41.0	40.2	39.3	37.8	35.9
Individuals registered at medical facilities						
in thousands	696.7	611.8	614.4	611.4	603.4	582.4
per 100,000 population	262	220	218	215	210	203

Morbidity rates for malignant neoplasms

	1980	1985	1986	1987	1988	1989
Individuals newly diagnosed						
in thousands	544	616	641	661	677.0	676.5
per 100,000 population						
without elimination of effect of age structure	205	222	229	234	237	236
with elimination of effect of age structure	243	261	268	270	271	268
Individuals registered at treatment-and-prevention facilities						
in thousands	2226	2635	2730	2833	2937	2816
per 100,000 population	836	946	971	997	1025	979

Individuals newly diagnosed with malignant neoplasm in 1989, by sex and age

		Per 100,000 population*		
Age, in years	Thousands	Both sexes	Male	Female
All ages	676.5	267.8	358.3	218.7
0-29	18.9	5.8	5.7	6.0
30-39	29.9	9.4	7.3	11.3
40-49	65.0	31.7	31.6	31.8
50-59	166.6	66.5	83.9	51.9
60 or older	396.1	154.4	229.8	117.7

Standardized indices with elimination of effect of population age structure.

Individuals newly diagnosed with malignant neoplasm in 1989, by tumor site

	Thousands			Per 100,000 Population*		
Site	Both sexes	Males	Females	Both sexes	Males	Females
All sites	676.5	341.3	335.2	267.8	358.3	218.7
Lips, oral cavity, pharynx	29.0	22.8	6.2	11.6	23.3	4.0
Esophagus	18.7	12.3	6.4	7.4	13.2	4.0
Stomach	94.4	53.8	40.6	37.5	57.1	25.6
Rectum, rectosignoidal junction, anus	29.2	13.1	16.1	11.5	14.2	10.2
Liver and intrahepatic bile ducts	14.8	8.4	6.4	5.8	9.0	4.0
Pancreas	20.0	10.3	9.7	7.9	11.1	6.0
Larynx	13.5	12.7	0.8	5.5	13.1	0.5
Trachea, bronchi, lungs	112.4	93.2	19.2	44.8	99.1	12.3
Skin	74.3	30.3	44.0	29.4	32.4	28.0
Breast (female)	53.1	-	53.1	21.4	-	37.0
Uterus	44.1	-	44.1	17.5	-	29.7

Individuals newly diagnosed with malignant neoplasm in 1989, by tumor site (Continued)

	Thousands			Per 100,000 Population*		
Prostate gland	10.6	10.6	-	4.2	12.1	
Bladder	15.4	12.3	3.1	6.1	13.5	1.9
Lymphatic and hemopoietic tissue	32.5	17.2	15.3	12.2	15.7	10.0

*With elimination of effect of age structure.

Morbidity rates for AIDS (at year's end)

	1988	1989	1990 (to 10 Oct)
All HIV-infected individuals in USSR	480	899	1104
HIV-infected Soviet citizens	113	428	553
All AIDS patients	8	26	51
Soviet citizens with AIDS	5	23	48
AIDS deaths among Soviet citizens	3	14	28

Morbidity rates for individual infectious diseases

	1980	1985	1986	1987	1988	1989
Number of cases, in thousands						
Typhoid and paratyphoid A, B, C	16.9	17.6	13.2	12.6	11.5	9.5
Other salmonellosis infections	110.4	76.3	76.5	96.1	133.5	156.6
All acute intestinal illnesses	1324	1601	1663	1702	1815	1464
Bacterial dysentery	464	620	545	558	605	392
Yersina infections	—	—	4.9	22.8	25.0	24.2
Brucellosis	3.5	5.1	5.4	5.4	5.1	5.3
Diphtheria	0.35	1.51	1.16	1.08	0.87	0.84
Whooping cough	14	54	18	20	45	37
Scarlet fever	230	278	357	330	215	225
Meningococcal infection	17.0	20.0	16.4	15.4	14.2	12.3
Cerebrospinal meningitis	8.1	8.1	6.3	5.9	5.3	4.7
Tetanus	0.30	0.28	0.26	0.19	0.20	0.20
Poliomyelitis	0.17	0.14	0.17	0.17	0.16	0.09
Chicken pox	1363	1645	1791	1712	1424	1596
Measles	356	273	165	191	165	52
Viral hepatitis	802	934	842	861	716	909
Serum hapatitis (B)	—	91	101	119	118	124
Epidemic parotitis	1027	490	545	358	200	165
Rickettsiosis	2.3	2.0	1.7	1.8	1.8	1.8
Epidemic typhus	1.1	0.5	0.4	0.4	0.4	0.3
Malaria	1.1	2.7	2.2	1.6	1.8	1.4
Influenza and acute upper respiratory infections	60,359	71,869	76,641	59,447	79,906	68,108
Number of cases per 100,000 population						
Typhoid and paratyphoid A, B, C	6	6	5	4	4	3
Other salmonellosis infections	41.6	27.5	27.3	34.0	46.8	54.6
All acute intestinal illnesses	499	578	594	602	636	511
Bacterial dysentery	175	224	195	197	212	137

Morbidity rates for individual infectious diseases (Continued)

	1980	1985	1986	1987	1988	1989
Yersina infections	—	—	1.8	8.1	8.8	8.5
Brucellosis	1.3	1.8	1.9	1.9	1.8	1.9
Diphtheria	0.13	0.55	0.41	0.38	0.30	0.29
Whooping cough	5	19	6	7	16	13
Scarlet fever	87	100	128	117	75	78
Meningococcal infection	6.4	7.2	5.9	5.4	5.0	4.3
Cerebrospinal meningitis	3.0	2.9	2.2	2.1	1.9	1.6
Tetanus	0.11	0.10	0.09	0.07	0.07	0.07
Poliomyelitis	0.06	0.05	0.06	0.06	0.06	0.03
Chicken pox	514	593	640	605	499	557
Measles	134	98	59	67	58	18
Viral hepatitis	302	337	301	305	251	317
Serum hapatitis (B)	—	33	36	42	41	43
Epidemic parotitis	387	177	195	127	70	58
Rickettsiosis	0.9	0.7	0.6	0.6	0.6	0.6
Epidemic typhus	0.4	0.2	0.2	0.1	0.1	0.1
Malaria	0.4	1.0	0.8	0.6	0.6	0.5
Influenza and acute upper respiratory infections	22,761	25,928	27,383	21,025	27,999	23,761

Sensory Memory Tasks and Personality Traits

917C0257A Moscow PSIKHOLOGICHESKIY ZHURNAL in Russian Vol 11 No 5, Sep-Oct 90 pp 27-31

[Article by N. N. Korzh, Ye. A. Lupenko and O. V. Safuanova, Institute of Psychology, USSR Academy of Sciences, Moscow]

[Abstract] An analysis was conducted on the impact of personality traits on sensory memory dynamics in the case of 40 healthy subjects ranging in age from 16 - 40 years in tasks requiring color (615.4 and 468 nm blue band) and sound (400 and 1000 Hz tones) recall. The subjects were represented by two groups: one consisting of professional musicians and artists and the other of individuals with no professional training in music or color schemes. The results showed that recall success was dependent on a complex of factors involving mnemonic strategies, descriptive techniques, past experience and perceptive capabilities. In particular, the emotional component of a given color or tone was seen to either facilitate or hinder recall, and was generally a more significant factor than past experience in determining accuracy of recall and persistence of memory. However, in indivudals with suboptimal sensory-perceptive mnemonic capabilities efficiency of recall was predicated on past experience with a given attribute. In such cases past experience served as a compensatory mechanism. References 25: 22 Russian, 3 Western.

Psychophysical Approach to Sensory-Perceptive Performance Vis-A-Vis Monotony and Fatigue

917C0257B Moscow PSIKHOLOGICHESKIY ZHURNAL in Russian Vol 11 No 5, Sep-Oct 90 pp 32-41

[Article by E. Z. Frishman, Institute of Psychology, USSR Academy of Sciences, Moscow]

[Abstract] Monotony and fatigue factors in the dynamics of visual differentiation were assessed in the case of 8 subjects, 18-30 years of age. Testing involved the digits '6' and '9' paired in four combinations (66, 69, 99, 96). The results demonstrated that in monotonous situations diminished visual differentiation occurs as a result of deterioration in perceptive mechanisms in combination with increasing inflexibility in decision-making. In the case of fatigue the mechanisms underlying impaired visual differentiation are attributable to diminished perceptive efficiency and increased laxity in decision-making. The data were interpreted to reflect reduced arousal in both situations. However, in cases of monotony, the task was perceived as a simple routine simplifying decision-making, whereas in fatigue, decision-making was affected by depletion of energy reserves. Figures 2; tables 1; references 27: 18 Russian, 9 Western.

Effect of Complex of Prophylactic Agents on Level of Content of Radioactive Cesium and Strontium in Organism of Laboratory Animals (White Rats)

917C0152 Moscow GIGIYENA I SANITARIYA in Russian No 10, Oct 90 pp 51-52

[Article by V. G. Bardov, G. M. Shmuter, B. P. Suchkov et al.; Kiev Medical Institute]

UDC 614.73:[546.36+546.42]-092.9-074

[Abstract] A study of the effect of some radioprotectors in different combinations on accumulation of radionuclides in the organism of laboratory white rats under actual conditions of their ingestion involved experiments on 130 + or - 10 g mongrel white rats kept in a vivarium on a standard diet with tap water for 100 days. Rats were placed in one of four groups. Groups 1-3 received a prophylactic drug with food in the following combinations and doses per individual rat. Group 1 - 50 mg of Prussian blue and 250 mg of methionine. Group 2 - 200 g of potassium orotate and 70 mg of calcium phosphate. Group 3 - 50 mg of citric acid and 50 mg of ascorbic acid and 100 mg of malic acid. Group 4 was the control group. At the end of the experiment rats were decapitated, the carcasses were incinerated and the radionuclides level was determined by radiochemical methods. Rats of all groups tolerated the experiment well, ate the additives readily and maintained weight comparable to that of the control group. Carcasses of group 1 rats contained the least ^{137}Cs. Addition of Prussian blue and methionine did not affect the ^{90}Sr level in the rats. Additives containing potassium and calcium promoted reduction of the radionuclides level: ^{137}Cs by 37.7 percent and ^{90}Sr by 20.2 percent. Addition of the organic acids significantly reduced the ^{90}Sr level in the rats but did not affect the ^{137}Cs level.

Effect of Prolonged X-Irradiation of Rats on Population Composition and Hemolytic Resistance of Peripheral Blood Erythrocytes

917C0206B MEDITSINSKAYA RADIOLOGIYA in Russian Vol 35 No 12, Dec 90 pp 30-31 (manuscript received 24 Mar 89)

[Article by B. F. Sukhomlinov, A. V. Trikulenko and L. A. Datsyuk; Lvov University imeni I. Franko]

UDC 612.111.014.418.1.08

[Abstract] A study of the population composition and hemolytic resistance of peripheral blood of rats on the 10th, 20th and 30th day after completion of 30-day chronic effect of X-irradiation in a daily dose of 0.258 mC/kg involved experiments on 10 (160-200 g) female mongrel white rats. Blood of control and experimental rats was taken from the caudal vein every 10 days after a 30-day effect of the X-irradiation. Erythrocytes separated from the heparinized blood, were centrifuged and washed three times by a sodium chloride physiological solution. Acid erythrocytes were produced by the Gitelzon and Terskov method. The population composition of the erythrocytes was studied by separation on a column with a saccharose density gradient. Separation of the erythrocytes revealed four populations of red cells of 1st, 2nd, 3rd and 4th fractions, situated in order of decrease of their densities. The content of these fractions did not change during the study. The acid resistance of the erythrocytes did not differ from that of the profile of the control group erythrocytes on the 10th and 20th days but it increased by the 30th day after cessation of chronic irradiation. Figure 1; references 5: Russian.

Microangiographic Study of Traumatized Liver in Acute Radiation Sickness

917C0206C Moscow MEDITSINSKAYA RADIOLOGIYA in Russian Vol 35 No 12, Dec 90 pp 31-34 (manuscript received Aug 89)

[Article by T. M. Mamadzhanov; Scientific Research Institute of Medical Radiology; USSR Academy of Medical Sciences; Obninsk]

UDC 616.36-001-06:616-001.28]-003.9-092.9

[Abstract] A study of the dynamics of vascular processes in damaged liver against a background of acute radiation sickness in order to establish its role in restorative processes involved experiments on 150 Wistar rats (wt 230-260 g) kept in an ordinary vivarium. Four groups of rats included: 1 - 20 intact rats (control group), 2 - 48 rats with liver trauma; 3 - 42 irradiated rats and 4 - 40 rats with combined radiation injury. A "Luch" (^{60}CO) device irradiated the rats with a 6 Gy dose. A special knife wound traumatized the liver. The microangiographic study followed the recommendations of the Scientific Research Institute of Medical Radiology, USSR Academy of Medical Sciences. Liver trauma produced coarse local impairments of hemocirculation immediately after infliction of the trauma and deterioration of the microcirculation outside of the traumatized lobe. Combined radiation injury produced phase changes in the hemocirculation. Soon after infliction of the trauma, there was liver parenchyma edema and impairment of the microcirculatory network. In the latent period, relative normalization of blood circulation occurred but, at the height of the injury, edema recurred with dilation of the vessels and hypostasis with subsequent rarefaction of the network and vasoconstriction of the vessels of the microcirculatory bed. Necrotic mass resorption proceeded as actively as in unirradiated animals. At the height of the lesion, increase of newly-formed capillaries stopped and necrotic masses were resorbed and this delayed restoration of the injured tissues. Figures 3; references 10: Russian.

Immunological and Blood-Transfusion Approaches to Limiting the Leukemia Stemming From the Accident at the Chernobyl Nuclear Electric Power Plant

917C0255A Moscow GEMATOLOGIYA I TRANSFUZIOLOGIYA in Russian Vol 35 No 12, Dec 90 (manuscript received 24 Nov 89) pp 4-7

[Article by Yu. M. Zaretskaya, All-Union Hematology Science Center, USSR Ministry of Health, Moscow]

UDC 616.155.392-02:614.875]-084

[Abstract] The incidence of radiation-induced leukemia, one of the long-term effects associated with the Chernobyl nuclear accident, can be expected to rise among those who were exposed at the accident site and among those in the path of the ensuing radioactive cloud—a total of some 230,000 individuals. The situation is complicated by indirect radiation exposure through the contamination of the environment by ^{136}Cs, ^{134}Cs, and ^{90}Sr, which enter the body through the food chain and create a hazard not only for those who consume contaminated products, but also for their progeny. Although the predictions by American researchers that some 100,000 individuals will develop leukemia by the year 2000 as a result of the Chernobyl accident is open to debate, there is no question that the long-term hematological effects of the accident will be on a massive scale in terms of the number of individuals affected and will require measures that affect large contingents of the population. The fact that those affected are generally from small families preclude any broad reliance on the use of bone marrow from relatives as a means of treating radiation injury to hematopoiesis. The strategy and tactics of measures aimed at limiting the effects of the accident must, therefore, be based on the classification of those injured into various risk groups based on immunogenetic markers. Bone-marrow transplantation must be based on the use of compatible, unrelated donors from the All-Union Register of Typed Donors. Proper tissue typing will be essential, as will transfusion measures that prevent complications associated with cytomeglaloviral infection. References 6: 2 Russian, 4 Western.

Determining Accumulated Doses of Gamma Radiation From Tooth Enamel

917C0255B Moscow GEMATOLOGIYA I TRANSFUZIOLOGIYA in Russian Vol 35 No 12, Dec 90 (manuscript received 2 Aug 90) pp 11-16

[Article by M. D. Brilliant (deceased), G. A. Klevezal, P. I. Mordvintsev, S. V. Khangulov, L. I. Sukhovskaya, V. A. Serezhenkov, N. V. Voyevodskaya, A. F. Vanin, Ye. V. Domracheva, N. Ye. Shklovskiy-Kordi, and USSR Academy of Medical Sciences Academician A. I. Vorobyev, Institute of Developmental Biology, USSR Academy of Sciences; Institute of Chemical Physics, USSR Academy of Sciences; All-Union Hematology Science Center, USSR Ministry of Health, Moscow]

UDC 614.73+614.876]-07:616.314.13-001.29-07

[Abstract] The fact that radiation-dose analysis from physical dosimetry is often not possible has prompted researchers to examine the feasibility of using biological techniques. Theoretical bases for the use of tooth enamel as a biological dosimeter hold that free electrons that appear in enamel after gamma or x-ray irradiation are trapped in crystal lattice defects, and the free radicals of carbonate that are formed can be recorded with EPR. Because the mineralization of the enamel makes such paramagnetic centers highly stable, the enamel preserves the history, as it were, of its radiation damage. The advent of computer technology has made it possible for EPR to detect threshold doses as low as 10 Gy. In verifying the feasibility of using tooth enamel to measure radiation dose, the researchers here irradiated teeth from Moscow stomatological clinics with ^{60}Co gamma radiation and with x-rays with a quantum energy of 0.12 MeV. Also studied was the enamel from teeth extracted from 85 inhabitants of various regions of Belorussia and from 31 Tomsk inhabitants. EPR signals were recorded via a Radiopan spectrometer with an MR-1092 computer. Signal intensity was a nonlinear function of sample mass in which ratio of measured amplitude (A) to sample mass (m) decreased as mass increased. The complex dependence of the internal standard EPR signal on sample mass in the resonator [$K(M)$] was described with two analytical expressions: $K(m) = 0.0026m+1.065$ for $m<$ 25 mg and $K(m) = 0.37+90.55/(m+119.71)$ for $m>$ 25mg. The quantity of radiation-induced paramagnetic centers per unit mass (I) in the enamel was estimated with the formula $I = A/mK(m)$. The value for Icould then be used to estimate the irradiation dose to the enamel from a calibration curve. Figures 4; references 19: 5 Russian, 14 Western.

Activity of Desoxyribonucleases of Blood Sera of Individuals Who Took Part in the Post-Accident Cleanup of the Chernobyl Nuclear Electric Power Plant

917C0255C Moscow GEMATOLOGIYA I TRANSFUZIOLOGIYA in Russian Vol 35 No 12, Dec 90 (manuscript received 2 Aug 90) pp 16-17

[Article by I. P. Moskalenko, N. A. Nikiforova, and I. Ya. Kalmykova, Scientific Research Institute of Medical Radiology, UkSSR Ministry of Health, Kharkov]

UDC 614.8767:]616.153.1:577.152.277]-074+612.128:577.152.277].014.482.4.06:614.876 CHERNOBYL

[Abstract] The destruction of radiosensitive cells is accompanied by the degradation of genetic material, with the entry of DNA decay products in the blood and urine. Researchers feel that desoxyribonucleases—whose elevated activity is noted in radiosensitive organs and blood serum after exposure to ionizing radiation—play a major role in those processes. Since the elevated activity is seen as a positive factor that helps the body properly

handle the decay products of nucleic acids, determination of the level of serum desoxyribonucleases can serve as an additional test for evaluating the body's protective responses. Two years after the Chernobyl accident, the researchers here studied serum levels in 90 individuals who took part in the cleanup and in 55 blood donors. They noted levels of DNAase I and DNAase II that were statistically significantly lower in the 90 individuals than in the donors. A substantial and steady decline was noted in only 18 individuals for DNAase I and in only 9 for DNAase II. Anamnesis in most of the individuals with lower desoxyribonuclease activity showed transient leukopenia and lower T-cell immunity phagocytic neutrophil activity. References 4: Russian.

State of Immunity Among Individuals Who Took Part in Post-Accident Cleanup at Chernobyl Nuclear Electric Power Plant

917C0255D Moscow GEMATOLOGIYA I TRANSFUZIOLOGIYA in Russian Vol 35 No 12, Dec 90 (manuscript received 2 Aug 90) pp 17-19

[Article by T. V. Kozyreva, N. A. Nikiforova, I. Ya. Kalmykova, Ye. S. Skobeltsyna, P. P. Sorochan, and A. N. Starodubtsev, Scientific Research Institute of Medical Radiology, UkSSR Ministry of Health, Kharkov]

UDC 616-092:612.017.1]-02:614.875]-07

[Abstract] Immune changes play an important role in the development of near-term and long-term effects of ionizing radiation. The researchers here studied the changes that took place in immunity indices in 57 individuals who took part in the Chernobyl cleanup from May 1986 to December 1986. The external radiation dose they were exposed to did not exceed 0.25 Gy. Average figures for leukocytes, relative and absolute lymphocytes, T-lymphocytes, and functional activity of T-lymphocytes were found to be normal both in 1986 (the first examination) and in 1989 (the second examination). IgM was found to be elevated in the second examination. The most informative findings were those pertaining to frequency of disturbances of immunity indices. Dynamic observation revealed that frequency of disturbance of bactericidal activity of neutrophils remained high (83 percent), as did that of the index of completeness of phagocytosis (87 percent). Disturbances in IgA and IgM levels tended to decline. The researchers made a comparison of frequency of identification of individuals with low functional activity of t-lymphocytes and level of reparative capacity of DNA of blood lymphocytes and then divided the Chernobyl cleanup crew members into two groups: those with a level of reparative capacity of less than 1.4, and those with a level of 1.4 or higher. They found that there were more individuals with low functional activity of T-lymphocytes in the first group than in the second. The researchers concluded that suppression of the capacity of lymphocytes of the peripheral blood to repair DNA is one of the factors leading to lower functional t-lymphocyte activity. References 10: 7 Russian, 3 Western.

Evaluation of Immune Status of Individuals Who Took Part in Post-Acccident Cleanup at Chernobyl Nuclear Electric Power Plant

917C0255E Moscow GEMATOLOGIYA I TRANSFUZIOLOGIYA in Russian Vol 35 No 12, Dec 90 (manuscript received 14 Jun 90) pp 19-20

[Article by T. V. Vorontsova, N. N. Galitskaya, Ye. N. Shavrova, G. M. Zhuk, R. M. Sharko, L. A. Khmelevskaya, and V. A. Ponomarev, Scientific Research Institute of Medical Radiology, UkSSR Ministry of Health, Kharkov]

UDC 616-092:612.017.1]-02:614.875]-078.33

[Abstract] One of the early signs of the effects of radiation on health is a change in the immune response of the body—e.g., allergies, higher susceptibility to infections, oncological diseases, and autoimmune disorders. The researchers here studied 65 individuals who took part in the Chernobyl cleanup. They evaluated immune status with a number of tests involving the state of T- and B-cell immunity, and they studied the nonspecific resistance of the body. Total number of T-lymphocytes and T-active lymphocytes in peripheral blood was estimated in the spontaneous E-rosette formation test with ram erythrocytes; for quantitative evaluation of basic subpopulations of T-helpers and T-suppressors, theophylline-dependent E-rosette formation was used. Quantity of B-lymphocytes was determined from total content of complementary rosettes. Serim immunoglobulin levels were determined with radial immunodiffusion; lysozyme levels, with a method described by Bukharin *et al.* All individuals were found to have a low percentage content of T-lymphocytes, although the absolute number was normal. Percentage content of theophylline-dependent and T-active lymphocytes was also low. A total of 20 individuals did exhibit low absolute levels of T-lymphocytes; 11 had high B-lymphocyte levels. The researchers compared immunity parameters against clinical diagnosis. Individuals with diseases of the gastrointestinal tract were more likely to have problems with T-system immunity; those with bronchopulmonary pathology, lower percentage content of B-lymphocytes, T-active and theophylline-dependent lymphocytes; those with neurocirculatory dystonia, lower percentage content of T- and T-active lymphocytes; and those with diagnoses ranging from diffuse encephalitis to osteochondrosis, normal values for immunity parameters. References 5: 2 Russian, 3 Western.

Prediction of Recovery After Whole-Body Irradiation From Hematological Indices as the Basis of Clinical Management of a Patient

917C0255F Moscow GEMATOLOGIYA I TRANSFUZIOLOGIYA in Russian Vol 35 No 12, Dec 90 (manuscript received 2 Aug 90) pp 27-31

[Article by Theodore M. Fliedner, Institute of Occupational and Social Medicine, Ulma University, FRG]

UDC 616.15-02:614.875]-037

[Abstract] Most physicians examining radiation-injured individuals do not have the proper quantitative data on hand pertaining to dose level and injury. The findings reported here involve the use of hematological indices such as quantity of granulocytes in relation to amount of time since irradiation to evaluate recovery prognosis. The key question to be answered in managing the patient is, is there a chance of spontaneous recovery of hemopoietic stem cells in a clinically acceptable time (2 - 3 weeks after exposure)? If the answer is yes, then so-called replacement therapy must be instituted. If no, then replacement therapy must include transplantation of hemopoietic stem cells. "Solution trees" can aid the development of a strategy for treatment in the context of sequential diagnostics. That must be done the first few days after exposure. Types of granulocyte dynamics must be linked to the extent of injury of hemopoietic stem cell pool. Figures 9; references 9: Western.

XII All-Union Conference of Roentgenologists and Radiologists (Summaries of Reports) IV. Radiobiology[1]

917C0317A Moscow MEDITSINSKAYA RADIOLOGIYA, in Russian Vol 35 No 10, Oct 90 pp 3-15

[Selected synopses of reports from 12th All-Union Conference of Roentgenologists and Radiologists]

[Text]

A. A. Akimov, A. P. Kozlov (Leningrad)

Problems in the Use of Isoeffective Models in the Radiation Therapy of Tumors

In the planning of a nonstandard schema of dose fractionation, the radiation therapist must foresee the possible radiation reactions of healthy tissues and tumors for the proposed course of irradiation. The empirical step formula of the NSD, or its algebraic modifications (DMF [dose modifying factor], IEC [isoexposure contour]), are utilized most often for this purpose. However, these isoeffective formulas overestimate the values of the tolerance doses for the hyper- and hypofractionation regimes. Some cellular kinetics models are of definite clinical interest. Thus, the two-component multitarget model in the Cohen version satisfactorily established the isoeffective doses for the hypofractionation schemas and split courses with a uniform rhythm of irradiation. The linear-quadratic model (LQM), which demonstrates differences in the reaction of rapidly proliferating and slowly divided tissues to fractionated doses, yields a good correspondence between the theoretical and experimentally obtained isoeffective doses for a wide range of normal tissues, irradiated with single doses of 2-10 Gy, distributed in 2-30 fractions with an interval of 24 h. Unfortunately, deviations in the established isoeffective doses from those predicted from the LQM do occur in courses of irradiation in 40-80 fractions with 24 hour fractionation of the dose. Which isoeffective model most adequately predicts the tolerance doses for such irradiation regimes has not yet been established.

In order to use isoeffective models for hyperfractionation, radiobiological investigations are needed which would permit the establishment of values of the per fraction doses below which the isoeffective total dose must not perceptibly increase. The minimal interval between the fractions for almost complete repair of sublethal injuries in limiting tissues also remains undetermined.

A. E. Antushevich, A. S. Petrov, A. N. Beloshapka (Leningrad)

The Influence of Ionizing Radiation on the Intensity of Purine Metabolism and the Processes of Peroxidative Oxidation of Lipids in Radiosensitive and Radioresistant Tissues

Xanthine oxidase (XO) is one of the most important enzymes linking purine metabolism with the processes of the peroxidative oxidation of lipids (POL). The data in the literature on the influence of ionizing radiation on the activity of XO of an irradiated organism are contradictory in character.

The experiments were carried out on white mongrel male rats, subjected to irradiation at a dose of 7.5 Gy (LD_{90}). The XO activity was determined on a the Impakt-400 biochemical analyzer, and the content of nucleotides, xanthine, and hypoxanthine was determined chromatographically on a Milikhrom chromatograph.

Under the influence of irradiation the XO activity increased in the thymus and the mucosa of the small intestine by a factor of 2 - 3.5 six hours after the irradiation, and in the liver, only after 24 h. The activation of XO was accompanied by radiosensitive tissues by the accumulation of products of free-radical POL reactions, diene conjugates and malondialdehyde, which may attest to the disruption of the integrity of the cell membranes.

On the basis of the material presented it is possible to draw the conclusion that the expressivity of the post-irradiation processes of degradation of purines to a large extent determines the death of radiosensitive cells.

V. N. Boyko, A. V. Stepanov (Leningrad)

A Study of the Radioprotective Properties of Ortofen [Orthophen]

Infectious complications arising as the result of the development of a secondary immunodeficiency are a principal cause of the death of animals following a radiation effect which induces the bone marrow form of acute radiation illness. For this reason the protection of the organism from infectious complications is one of the urgent lines of investigation in contemporary radiobiology.

In this study an indole derivative, the preparation, ortofen [orthophen], which is classified as a prostaglandin synthesis inhibitor, was investigated. This compound exerts an analgesic and anti-inflammatory effect. The represntatives of this class are especially effective in various autoimmune diseases, and are modulators of nonspecific resistance.

The experiments were carried out in 400 mongrel male mice,weighing 18-22 g, subjected to total irradiation in a dose of 6 Gy. The ortofen was administered in a single dose of 20 μg per mouse and in three doses according to protocol (20 μg per mouse every hour for three hours). The preparation was used 1 day [sic] and 1, 3, or 5 days after irradiation.

The one-time administration of ortofen was of little effect in all the periods investigated. The administration according to the protocol of 1 day before and 1 day after irradiation increased the survival of the irradiated animals by 30-40 percent as compared with the control, as well as the average life span of the animals. The administration of ortofen 3.5 days after the radiation effect was minimally effective.

The radioprotective action of ortofen is explained by its influence on the functional activity of phagocytic cells.

L. P. Vartanyan, G. F. Gornayeva, G. N. Krutovskikh, YU. I. Pustovalov, T. V. Barskaya (Leningrad)

Increasing the Effectiveness of Radiation Therapy of Experimental Neoplasms by Means of Allopurinol

It is known that allopurinol enhances the antitumor effect and decreases the toxicity of a number of cytostatic agents. Our own experimental investigations have demonstrated that allopurinol exerts a pronounced stimulating effect on the hematopoiesis of irradiated animals, and have also revealed its capacity to inhibit the repair of radiation-induced breaks in DNA, which has enabled us to hypothesize the radiosensitizing property of this preparation. The results of experiments on animals with several strains of transplanted tumors of varied histogenesis have shown that allopurinol provides a radiosensitizing effect not less than the action of metronidazole. The preparation is active both in the case of a one-time irradiation and in the case of various regimes of fractionated irradiation.

The aggregate of the data known from the literature and the experimental data we have obtained characterizes allopurinol as a low-toxicity compound possessing a wide spectrum of biological activity. A clinical study is currently being carried out of allopurinol as a radiosensitizer of tumors in the radiation therapy of a number of neoplasms.

V. R. Virabov, I. E. Melikyan, R. K. Oganesyan, I. S. Stepanyan, G. M. Tiroyan, K. V. Asryan, M. M. Zagaryan, M. L. Melkonyan (Erevan)

Results of a Dynamic Observation of Residents of the Armenian SSR Who Had Participated in the Elimination of the Consequences of the Accident at the ChernobyL NPP

The purpose of the present investigation was a study of the changes developing in the organism of individuals subjected to the effect of low levels of radiation during the elimination of the consequences of the accident at the Chernobyl NPP.

One thousand forty-three individuals were subjected to examination. The dose of external irradiation, according to the information presented, was 10-45 rem.

In addition to careful clinical laboratory testing, a biological assessment of the post-irradiation changes was carried out by the densitogeometric method, the immune status was determined, and the state of peripheral tissue blood flow was evaluated.

Functional diseases of the nervous and cardiovascular systems were diagnosed most frequently (69 percent), as well as diseases of the gastrointestinal tract (41 percent), osteochondroses (44 percent), and diseases of the respiratory organs (20 percent).

When the morbidity of the subjects was analyzed, no distinct patterns were revealed as a function of the dose of radiation,the period and duration of work at the Chernobyl NPP, or professionally harmful practices.

Functional disorders of the central nervous system, the hypokinetic type of reaction of the cardiovascular system to a physical load, a decrease in reserve blood flow to muscles, a lowering of the immune status,and some hematologic and biochemical alterations formed the basis of the pathological changes in these individuals.

Characteristic changes for a radiation effect were identified in 69 percent of cases 1-18 months following irradiation through karyometric analysis of peripheral blood lymphocytes.

A decrease in the frequency of the functional disorders and a decrease in the frequency of chronic organic diseases were established in the time course in these subjects.

A. A. Volkov*, V. M. Zaytsev, A. B. Markochev, I. YU. Savicheva, V. B. Nizkovolos, E. G. Alekseev (Leningrad)

Experimental Evaluation of the Diagnostic Possibilities of ^{123}I-Labeled Fatty Acids

The extremely important role of the fatty acids in the energy supply of cardiac muscle and their capacity to be extracted intensively by the myocardium underlie the development of the scintigraphic methods for the investigation of the heart. The labeling of fatty acids with various isotopes of iodine are used for the scintigraphy. Due to its physical properties (monoenergetic γ-radiation of 159 keV, short half-life of 13.3 h), ^{123}I is the most suitable isotope for scintigraphy with a marker

which permits the decreasing of the radiation burden on the patient and the obtaining of high-quality scintigrams.

The utilization of ^{123}I-labeled fatty acids permits the visual assessment of blood flow in the coronary arteries, and the obtaining of quantitative data regarding the state of the metabolic processes in the myocardium.

Experimental investigations were carried out, as the result of which the high radiochemical purity of the new diagnostic preparations, ^{123}I-pentadecanoic acids and ^{123}I-phenylpentadecanoic acids, the harmlessness for the organism of the animals studied, and the good diagnostic possibilities in the assessment of the metabolic and blood flow in the myocardium, were demonstrated.

A. I. Volozhin, N. G. Davydova (Moscow)

The Influence of X-Irradiation and Gamma Radiation on the Osseous Tissue of Various Division of the Skeleton of Dogs

Ten dogs were subjected to total X-irradiation in a dose of 4 Gy from an RUM-17 apparatus (180 kV, dose rate 20 rad/min, filter 0.5 mm Cu); seven dogs were subjected to γ-irradiation in a dose of 3.6 Gy from an EGO-2 unit, dose rate 27.27 rad/min; 15 dogs served as control. The dogs died as the result of the development of acute radiation disease in 14-25 days. Fragments of the diaphysis and the distal epiphysis were sawed from the femur, from the jaws, namely the interdental and the inter-root partitions in the region of the front and masticatory teeth. The mechanical properties of the fragments were determined, as well as the biophysical characteristics and the elemental composition of the bone ash.

The X-irradiation led to a decrease in the ultimate strength of the fragment of the distal epiphysis of the femur by 24.9 percent; following γ-irradiation the mechanical properties of these structures decreased only by 12.4 percent. the stregth properties of the cortical bony tissue of the diaphysis did not change. In the lower jaw the most marked changes occurred in the interdental partitions of the front and masticatory teeth, and particularly in the case of the action of the X-irradiation. The changes in the mechanical properties were accompanied by corresponding changes in the mineral component. Thus, the mineral saturation of the spongy tissue of the dogs' femur decreased under the influence of X-irradiation by 19.8 percent, in the region of the interdental partitions in the region of the front teeth, by 3.2 percent, and of the masticatory teeth, by 6.5 percent. Following the exposure to the γ-radiation the changes in the mineral saturation were 7.4, 9.8,and 5.6 percent, respectively.

A.V. Ganul, V. A. Zinchenko (Kiev)

The Inhibition of DNA Synthesis in Thymoma Cells With the Modifying Influence of UHF Hyperthermia

The death of cells in the presence of irradiation modified by hyperthermia is largely determined by disruption of the structure and function of DNA.

The tissue of malignant thymic tumors of 16 patients was studied in diffusion chambers. The tumors of seven patients were irradiated in combination with UHF hyperthermia; the tumors of three patients were subjected to radiation therapy alone; the postoperative intact tumor material of nine patients served as the control. The tumors in three patients were studied before and after the exposure. The total irradiation dose was 20 Gy. The source of the electromagnetic radiation was a modified Volna-2 (460 MHz). The temperature during the hyperthermia was 42°-45°C.

In the majority of the preparations of the control thymuses, which were not subjected to the physical influence, intensive growth of the explant was observed. The labeling index was found to be on the average at 11.6 +/-3.4 percent level. In the irradiated tissue of the cultivated thymomas, in addition to the marked polymorphism, four types of subpopulations were found among the DNA-synthesizing cells. The number of DNA-synthesizing cells decreased under the influence of irradiation down to 5.1 +/- 1.2 percent.

The combined influence of the hyperthermia and the radiation on the thymoma cells led to a significant decrease in the DNA-synthesizing fraction of the cells, and in survival, even in those cases in which the growth of epithelial-like cells was recorded in the zone of proliferation. The growth of cells was not observed in the tumor preparations of seven out of nine dogs. In two other cases the multiplication of cells was recorded in only six out of 24 chambers. The labeling index in these was found to be at a low level, 1.4 +/- 0.2 percent.

L. M. Gunina, E. A. Fedorenko (Kiev)

The Activity of DNAase I and the Factors of Local Humoral Regulation During Neutron Irradiation

In this study the influence of local fractionated irradiation with fast-neutrons with an energy of 6 MeV on the activity of DNAase I and of its inhibitor, and on the kallikrein kinin system (KKS) of the blood was evaluated in an experiment on 46 rats with Guaerin's carcinoma (total dose 6 Gy) and in 22 patients with tumors of the head and neck and the locomotor system (4.2-6 Gy).

An increase in DNAase I activity and in the activity of its inhibitor by a factor of 1.5 - 2 was observed in the blood of the rats 15 days after the irradiation. The exposure to radiation leads to a disruption of the complex-formation of the enzyme with the inhibitor, and the degree of DNAase I activity was pronounced to a greater degree with exposure to densely ionizing radiation as compared with sparsely ionizing radiation. The level of DNAase

and of its inhibitor did not substantially differ from the initial level one month after the irradiation with neutrons.

An intensification of the formation and inhibition of the breakdown of kinins, with the predominance of the processes of synthesis, is observed in the blood of the irradiated animals after 15 days. At the same time, a decrease is observed in the content of proteolysis inhibitors and of kininogen, which leads to the accumulation of free kinins in the blood and the prolongation of their effect. The increase in the concentration of free kinins in the circulating blood is accompanied by an increase in the permeability of microvessels, and by an intensification of tissue blood flow.

Changes of a similar direction were also established in the oncological patients with neutron irradiation.

There is a correlation between the DNAase level and the degree of activation of kininogenesis ($r = 0.72$, $p < 0.05$). The introduction of inhibitors of kinin-formation directly into the tumor (contrical) experimentally decreases the effectiveness of neutron therapy. Taking into account the possible role of DNAase in the destruction of tumor cells under the influence of irradiation (Reske, et al., 1983), the activation of the KKS may favorably influence this process.

I. N. Dimant, M. M. Satayev, G. M. Loktinov (Tashkent)

The Histogenesis of Radiation-Induced Brain Neoplasms

The creation of experimental models of radiation-induced brain neoplasms, which is of definite interest in and of itself for this division of oncology, is simultaneously of no little theoretical significance in general pathological terms.

Sources of ionizing radiation (granules of ^{90}Co and ^{90}Sr-^{90}Y), with different irradiation dose rates were implanted into the brain of 115 rabbits. In periods of 226-920 days (at absorbed doses of 75-950 Gy), connective tissue neoplasms fo uniform morphological structure formed around the sources in 34 experimental animals (more than 30 percent). It was established in histological and electron microscopic investigations that these tumors are constructed of elements of mesenchymal origin of different degrees of maturity, from epithelial-like and epithelioid cells up to osteocytes. The presence of the later in the tumors is, according to our notions, evidence of their development at the stages of cell differentiation of cell elements which participate in the reparative reaction to irradiation (which is also confirmed by observations of the time course of this process during the investigation at 1, 3, 6, 9, 12, and 15 months from the beginning of the experiment).

Analysis of the results obtained argue in favor of the thesis that in these experimental conditions, the development of mesenchymal brain neoplasms is governed mainly not by radiation-induced mutations, but by epigenomic changes which induce depression of the genome which controls the proliferation and the differentiation of the cellular elements of the mesenchyme.

Our hypotheses are in complete agreement with those notions previously advanced by S. N. Aleksandrov (1972) regarding the pathogenetic mechanisms of the development of radiation-induced tumors.

A. Kh. Dosakhanov, Kh. A. Akhmetbekova, A. Kh. Khamzin, S. B. Balmukhanov (Alma-Ata)

Hyperthermia in the Polyradiomodification System in the Comprehensive Therapy of Esophageal Cancer

One hundred eighty-one patients with esophageal cancer were subjected to radiation therapy: the first group (control, of 52 patients who were treated only with radiation therapy); a second group of 67 patients, treated with radiation therapy and with the use of brief induced hyperglycemia (BIG); a third group of 30 patients, irradiation plus the use of UHF hyperthermia (HT); and fourth group of 32 patients, irradiation under conditions of polyradiomodification (combination of HT and BIG). Squamous cell cancer of varying degrees of maturity was identified in all the patients. In the main (93.9 percent of patients), these were patients with stage III disease; stage II disease was identified in 2.7 percent of the patients, and stage IV disease was identified in 3.3 percent of the patients.

The radiation therapy was carried out in all groups in two steps by the method of dynamic fractionation: step I consists of the irradiation of the esophagus with 4 Gy every other day up to a total focal dose (TFD) of 32 Gy; after a 10 day break, step II, consisting of irradiation twice a day with 1.25 Gy per session. The TFD for the whole course was 58-60 Gy.

When post-radiation BIG is carried out (6-8 sessions) on the radiation days at step I of the radiation therapy, the glucose level in the blood was maintained in the range of 23-30 mmole/l. The Plot, Yakhta-3, and Volna-2 units with an operative frequency of 460 or 915 Hz, with flexible UHF radiators, diameter 8-10 mm, were used for local heating of the tumor prior to irradiation. The temperature at the surface of the tumor was maintained at the level of 42.5°-43.7°C for 45-60 min.

The direct results of the therapy were evaluated on the basis of the degree of tumor regression, determined X-ray radiometrically and endoscopically: complete regression was observed in the control group in 36.5 +/- 2.9 percent of patients, marked regression in 32.6 +/- 2.6 percent of patients, partial regression in 23 +/- 2.8 percent of patients; there was no effect in 7.6 +/- 1.8 percent of patients; in the second group, in 40.2 +/- 4.1, 41.7 +/- 2.3, 16.4 +/- 1.9, and 1.4 +/- 0.9 percent of patients, respectively; in the third group, complete, marked, and partial regression of the neoplasms was identified in 46.7 +/-3.5, 40.0 +/- 3.5, and 13.3 +/- 2.1 percent of patients, respectively; and in the fourth group,

in 56.3 +/- 4.8, 34.3 +/- 4.1, and 9.4 +/- 3.5 percent of patients. There were no patients without a treatment effect when HT and/or polyradiomodification were used.

V. I. Yevtushenko, O. V. Barabitskaya, A. E. Borovitskaya, K. P. Hanson (Leningrad)

The Use of DNA Probes for the Study of Post-Radiation Disturbances of the Processes of Development, Differentiation, and Regeneration

Cloned sequences of genes labeled by means of ^{32}P or ^{33}P-NTP were used to determine the level of expression in tissues of irradiated animals. The following objects were studied: the developing brain and liver, the regenerating liver, and differentiating thymic lymphocytes. The following groups of cloned genes were used as probes: protooncogenes, tissue-specific genes, and "housekeeping" genes. The prenatal irradiation of the rats elicits the activation of the expression of a number of protooncogenes and tissue-specific genes in the brain and liver of the postnatally developing animals. Thus, the content of transcripts of the genes of serum albumin, α-macroglobulin, and ATPase was increased in the liver in the newborns. In the regenerating liver, γ-irradiation (5 Gy) suppresses the expression of these genes. By contrast, irradiation elicits a brief activation of the protooncogene fos in both cases. The intensification of the expression of these genes of the neurofilaments, the principal protein of myelin, proteolipid, and fos in the developing brain of prenatally irradiated rats coincides with the period of active differentiation of the neurons. Brief activation of the genes Thy-1, TdT, and CD8, and protooncogenes fos, Ha-ras, and myb is observed 0.5 - 2 h following in irradiation (4 Gy) the differentiating thymic lymphocytes. A subsequent decrease in the expression of these genes is associated with the death of the irradiated thymocytes.

S. A. Ermekova, G. O. Eselbayeva (Alma-Ata)

The Influence of Mercaptopurine and its Combination With Metronidazole on the Radiosensitivity of Pliss Lymphosarcoma

In order to intensify the effect of radiation on Pliss lymphosarcoma, the following were tested: mercaptopurine in a dose of 5 mg/kg, administered through an esophageal sound prior to irradiation; metronidazole in a dose of 700 mg/kg 2 h prior to irradiation, and the combination of metronidazole, mercaptopurine, and irradiation. The fractionated irradiation in a single dose of 4 Gy was carried out six times every other day to a total dose of 24 Gy.

Intensification of the retardation of tumor growth was observed in all groups of combined irradiation: in the case of a single irradiation, 40 percent; in the combination mercaptopurine+metronidazole+irradiation, 84 percent; and in the case of a single dose of metronidazole and irradiation, 94 percent.

The synthesis of DNA (based on the incorporation of ^{3}H-thymidine) is substantially blocked 1 h after irradiation, and to a lesser degree after irradiation in combination with mercaptopurine, and with irradiation against the background of metronidazole and mercaptopurine.

Prolonged profound block of DNA synthesis is observed in the group involving irradiation against the background of mercaptopurine. Additional administration of metronidazole partially removes the block of DNA synthesis necessary for the repair of radiation injuries.

Thus, the removal of the post-radiation block of DNA synthesis by mercaptopurine and metronidazole intensifies the injurious effect of irradiation.

V. N. Zilfyan, V. A. Kumkumadzhyan, A. K. Nersesyan (Erevan)

The Intensification of the Antitumor Effect of Radiation Therapy by Immunization of Rats With Tularemia Vaccine

We have previously demonstrated that the immunization of white rats with tularemia vaccine (TV) 15 days before total irradiation in a dose equal to the $LD_{50/30}$ increases the radioresistance of the animals.

On the basis of these data, it seemed of interest also to elucidate the kind of effect TV would exert during the radiation therapy of malignant tumors, all the more so since this vaccine in our experiments yielded positive results in the chemotherapy of these diseases.

In the present report we present the results of experiments carried out in mongrel rats with Pliss lymphosarcoma, immunized 15 days prior to the transplantation of the tumor. The tumor was subjected to local irradiation by means of an RUM-17 apparatus in a dose of 7 Gy, every other day, five times. The effectiveness of the treatment was evaluated 15 days after transplantation on the basis of the inhibition index.

The results of the experiments showed that immunization leads to a decrease in tumor mass by a factor of 2.3, irradiation by a factor of 4.1, and both factors together, by a factor of 6.8 as compared with the control.

Thus, the preliminary immunization of rats with TV increases the radioresistance of the organism and the antitumor effectiveness of the radiation therapy. We expect that TV can be used to increase the effectiveness of radiation therapy of some forms of malignant neoplasms.

L. A. Zotikov, Z. N. Petrenko, T. P. Segeda, K. A. Galakhin, P. A. Maligonov, A. V. Ganul, V. O. Kikot (Kiev)

Ultrastructural Changes in the Cells of a Human Tumor With Radiation Therapy, UHF Hyperthermia, and Their Combination

The pathomorphosis of tumors of the stomach, large intestine, and thymus was investigated by transmission

electron microscopy in patients undergoing gamma-therapy and local UHF hyperthermia. The tissue of biopsy material from the tumors prior to treatment, 2 h after the first session of radiation therapy, hyperthermia, and the combination of both factors, as well as tissue of some tumors upon completion of the course of treatment, was studied. The radiation therapy was carried out by means of a ROKUS apparatus in the static regime in a single dose of 5 Gy, the UHF hyperthermia locally by means of a Volna apparatus at a frequency of 460 MHz for 1 h. The temperature, controlled by thermocouples, reached 42.5°-43.5°C in the tumors.

The form and intensity of the initial manifestations of dystrophy and necrobiosis of the ultrastructures of the cancer cells differed with the various methods of preoperative therapeutic influence. The irradiation induces first and foremost the activation of the lysosomes and pycnosis of the nuclei or local lysis of the nucleolema without the exiting of the contents of the nucleoplasm. Hyperthermia elicits primarily vacuolization of the cytoplasm and the structural disorganization of the protein-synthesizing apparatus (of the polysomes and the granular endoplasmic reticulum). In the case of the combined influence of both factors, the combination of these effects is observed, and the number of tumor cells dying increases relatively, i. e., transformations of the coagulation type are more characteristic for the radiation therapy, while for hyperthermia, the colliquation type is more characteristic. The combination of remedial factors leads to subcellular disturbances of varied character.

Unpon completion of the course of therapy, it was established electron microscopically that a greater destruction of the parenchyma of the tumor and its replacement with stroma takes place with the combined therapy, with a smaller dose of the gamma component.

Yu. P. Istomin, B. D. Shitikov (Minsk)

A Radionuclide Investigation of Blood Flow in Various Tumors of Rats With Artificial Hyperglycemia

It has been demonstrated in white mongrel rats with Walker-256 carcinosarcoma and sarcoma 45 that the degree of the decrease and subsequent restoration of pH in tumors observed during hyperglycemia (intravenous infusion of glucose, 12 g/kg in 3 h) depends on the reversibility of the disturbance in blood flow.

A comprehensive assessment of the state of the hemodynamics in the presence of artificial hyperglycemia (AH) was accomplished in a Sigma 410-C gamma chamber. Simultaneously with the injection into a vein of 74 MBq of ^{99m}Tc-albumin (TCK-2, Sorine, France) in a volume of 0.2 - 0.5 ml, the data on the rate and quantity of the inflow of the radiopharmaceutical was recorded by means of the recording system of a computer (VP-450) over the course of 2 sec (1 frame/sec).

When the angioscintigrams are analyzed comparatively, the features of the systemic effect of the AH on the organism of the tumor-bearing animals are identified, as is the reactivity of the microvascular bed of the Walker-256 carcinosarcoma and sarcoma 45, which varies in the degree of expressivity.

The maximal inhibition of the rate of blood flow with respect to all the parameters investigated was recorded in the rats with the Walker-256 carcinosarcoma by the moment of the ending of the glucose infusion. For example, the rate of accumulation of the radiopharmaceutical decreased in the tumor from 3.65 +/- 0.9 to 0.78 +/- 0.2 imp/sec, and in the symmetrical zone, from 3.97 +/- 0.9 to 1.72 +/- 0.5 imp/sec. Subsequently, after 5 and 24 h, an increase in these values was observed in the tumor up to 1.44 +/-0.39 and 4.4 +/- 1.4 imp/sec, and in the symmetrical zone, to 2.22 +/- 0.34 and 4.36 +/- 0.9 imp/sec, respectively.

In animals with sarcoma 45, a worsening of blood flow was established in all periods of observation, with a maximal decrease by the fifth hour after the ending of the artificial hyperglycemia. By this time the rate of accumulation of the radiopharmaceutical in the tumor had decreased from 3.8 +/- 0.8 to 0.15 +/- 0.05 imp/sec, and in the symmetrical zone, from 4.1 +/- 0.7 to 0.35 +/- 0.05 imp/sec, remaining lower than the initial also after 24 h (3.42 +/- 0.4 in the tumor and 3.9 +/- 1.04 imp/sec in the symmetrical zone).

In our opinion, the nonidentical capacity of the cells of the tumors in question to metabolize glucose coming from the outside, which leads to a nonidentical degree of inhibition of blood flow and a decrease in pH, underlies the differences obtained. This dictates the necessity of developing individual indications for the use of AH as a radiomodifying factor.

Yu. P. Istomin, A. V. Furmanchuk, V. Z. Rubanova (Minsk)

A Study of the Possibility of Intensifying the Antitumor Effect of Ionizing Radiation by Means of Artificial Hyperglycemia and Local Hypoxia

In experiments on white mongrel rats with Walker-256 carcinosarcoma and healthy animals, we carried out a comparative study of the state of the acid-base balance, the dynamics of changes in the pH in the tumor and normal tissues (microelectrode measurement), the average life span of the animals which succumbed and the percent of cured animals, and the morphological changes in the tumor with artificial hyperglycemia, local hypoxia, radiation in doses of 10, 15, and 20 Gy on a one-time basis, as well as with the combination of these influences.

Neither artificial hyperglycemia (intravenous infusion of a glucose solution in a dose of 4 g/kg per hour over the course of 160 min) nor local hypoxia (tourniquet on the extremity for 60 min above the zone of tumor growth), nor the combination of these two factors yielded any remedial effect.

The creation of post-radiation hypoxia immediately after the irradiation induced a significant increase in the percent of animals cured and an increase in the amounts of autolytic degeneration of the neoplastic cells.

Even though the combined use of all three types of influences led to significant shifts in the acid-base balance of the blood and an increase in the difference in pH between the tumor and normal tissue, it was nevertheless not possible to achieve more extensive destruction of the Walker-256 carcinosarcoma or a higher percent of cure of the animals. In our view, this can be explained by the insufficient degree of glycolytic activity of the cells of the tumors used in this experiment, which confirms the need to look for means to individualize the indications for the use of artificial hyperglycemia.

P. Kazymbetov (Moscow)

The Effectiveness of the Combined Use of Sulfur-Containing Radioprotectors and a Hypoxic Mixture (8% O_2) in Fractionated Irradiation

The use of chemical protectors in clinical practice for the purpose of the preferential protection of normal tissues during the radiation therapy of malignant neoplasms has not received wide dissemination, despite the large amount of experimental research which has been done. Analysis of the literature shows that the inadequate effectiveness of the majority of them in doses tolerated by man has impeded the introduction of the protectors.

In the present study we have investigated the effectiveness of the protection of normal and tumor tissues by small doses of cystamine (200 mg/kg by mouth) and gammaphos (264 mg/kg intramuscularly) under conditions of the breathing of a hypoxic (8% O_2) mixture by mice.The quantitative assessment of the radioprotective effect was carried out simultaneously on the basis of the post-radiation retardation of the solid Ehrlich carcinoma and the early radiation reactions of the skin falling within the zone of irradiation. The dose change factor (DCF) for the skin and the tumor was calculated as the ratio of the isoeffective doses of irradiation of the experimental and control groups.

The protective effect of gammaphos and cystamine for the skin with one-time irradiation was small; the DCF was 1.14 and 1.09, respectively, while these radioprotectors exerted no influence on the antitumor effect of the radiation. The effectiveness of the hypoxic mixture for the skin was more pronounced; the DCF was 1.28, while protection of the tumor was not observed.

When the protectors were administered before each session of a five-time daily local irradiation, significant protection of the skin was observed. The DCF cystamine and gammaphos were 1.16 and 1.31, respectively, whereas the protection of the tumor was insignificant. The combined use of gammaphos or cystamine with hypoxic conditions promotes a still more pronounced protection of the skin: the DCF increased to 1.62 and 1.78, respectively; at the same time the protection of the tumor remains small; the DCF measured at the level of a 30-day lag in the growth of the tumor was 1.1.

Thus, with fractionated irradiation the use of protectors under conditions of exogenous hypoxia leads to an increase in therapeutic benefit.

D. N. Kachurina, M. M. Valshteyn (Minsk)

A Therapeutic Gain Factor With the Combined Influence of Hyperglycemia, Hyperthermia, and Irradiation

The search for possibilities for controlling radiosensitivity is one of the central problems of the combined treatment of malignant tumors. At the same time, the danger of extreme injury to normal tissues is a limiting factor in the obtaining of the maximal antitumor effect. Therefore, the contemporary treatment of malignant tumors is built on a compromise, the achievement of the maximal antitumor effect with tolerable injury to normal tissues.

The purpose of this study was the assessment of the influence of some regimens of the combined influence of hyperthermia, irradiation, and hyperglycemia on normal and tumor tissues.

The reaction of sarcoma 45 and the skin to one-time irradiation in doses of 20, 30, and 40 Gy was studied in an experiment on 340 rats under conditions of neuroleptanalgesia, as well as of the combined influence of hyperthermia of 43.2°C (60 min), irradiation in a dose of 34.6 Gy, and hyperglycemia, produced by the intraperitoneal administration of glucose in a dose of 6 g/kg. The thermoradiotherapy and the radiothermotherapy were carried out before the administration of glucose or 1 h after it.

The kinetics of tumor growth, the cure rate, and the radiation reactions of the skin above the tumor were studied. The dose change factor (DCF) for the tumor and the skin and the therapeutic gain factor (TGF) were calculated.

Irradiation in a dose of 34.6 Gy elicited a decrease in the rate of tumor growth, and led to cure of 22.6 percent.

The suggested protocol of combined influences proved to be highly effective according to all the assessment criteria: the DCF for the skin was 0.9, for the tumor, 1.73; the TGF was 1.92; the cure rate, 79 percent.

L. P. Kindzelskiy, L. A. Zotikov, Z. N. Petrenko, K. A. Galakhin, B. Ya. Goldshmid, V. A. Zinchenko (Kiev)

The Influence of Combined Radiation on the Bone Marrow and the Gastric Mucosa of Human Beings (Ultrastructural and Histoautoradiographic Aspects)

Individuals who found themselves in the zone of increased radiation in April-May 1986 as the result of the accident at the Chernobyl NPP were subjected to investigation.

Tissue material obtained through sterile punctures from 23 individuals and gastric biopsy from 15 individuals was processed by means of the traditional method for electron microscopy, including mounting in Epon.

Hypoplasia of the bone marrow of varying degree and the replacement of its parenchyma by fatty tissue was established in almost all subjects with the diagnosis of "acute radiation disease". The saturation of the macrophages and reticular cells with small polymorphic vacuoles with very dense homogeneous contents was observed in the majority of cases. Extensive and marked changes were found in the endotheliocytes, with disruption of the integrity of the membrane of the capillaries and the sinusoids of the bone marrow.

Ultrastructural changes were found also in all types of epithelial cells of the gastric mucosa; the dystrophic, necrotic, dysplastic, and proliferative processes present were expressed in different degrees in each individual case. Total destruction of all the cellular elements of the stroma with karyopycnosis and/or karyorrhexis, and extensive foci of intracytoplasmic lysis had taken place in a number of cases. Marked vacuolization of the endotheliocytes was observed.

The electron microscopic changes correlate with the results of autoradiographic analysis, which demonstrate the accumulation of radionuclides in the bone marrow and the gastric mucosa. Radioautographic images of the radioactive particles were visualized in the form of grains and tracks, which indicates the localization of a mixture of radionuclides in the organs.

E. N. Kirillova, L. D. Murzina, V. S. Voronin, K. N. Muksinova (Moscow)

The Quantitative Patterns of the Dynamics of Immunocompetent Cells With Various Schedules of Prolonged γ-Radiation

The dynamics of the cell count in the lymphoid organs (thymus, spleen, lymph nodes) were compared, in experiments on Wistar rats and mice of the CBA line, subjected to irradiation in doses of 0.5 - 30 Gy (dose rates 4.5 - 50 cGy/day), with the number of lymphocytes in the bone marrow and the peripheral blood, as well as with the magnitude of the indices characterizing the state of humoral (number of antibody-forming cells, the functional activity of effectors and regulators of the immune response to antigen) and cellular (the cytotoxic activity of natural killers) immunity. A relationship of the degree of destruction of the lymphoid organs, their residual hypoplasia at remote periods, and the deficit of lymphocytes in the bone marrow and the blood on the magnitude of daily and total radiation doses was identified. The character of the dynamics of the number of lymphocytes in the central and peripheral organs of immunity depended on the irradiation schedule.

The disturbance of the immune processes with chronic irradiation was caused by the hypoplasia of the lymphoid tissue, the degree of which depended on the magnitude of the depopulation of the divisions of polycompetent and committed precursors of the lymphocytes. The identified quantitative patterns of the injury of lymphoid organs will be utilized for the forecasting of the stochastic and nonstochastic effects of external irradiation.

L. I. Kovaleva (Moscow)

Functional Tests in the Identification of Vegetative Dysfunction in Workers Participating in the Elimination of the Consequences of the Accident at the Chernobyl NPP

We examined 122 individuals (116 men and 6 women), aged 19-58 years, of whom 103 were younger than 40 years. Eighty individuals had participated in the elimination of the consequences of the accident in 1986 (average dose 0.24 Gy); the rest had done this work in 1987 and 1988 (0.09 Gy). The dose was not established in some of the subjects. In the analysis of the ECG, our attention was drawn to the frequency of bradycardia (47.5 percent) and ectopic precordial rhythm (12.3 percent). An increase in the T wave and its widening in chest leads was observed in 62.3 percent of the subjects; a decrease in the ST interval was observed in 71.3 percent. A difference was not obtained in the frequency of these as a function of dose. In order to define more precisely the nature of the vagotonia, the patients were subjected to physiological and pharmacological tests. The physiological tests and the intravenous administration of atropine, which elicited an in significant acceleration of rhythm, pointed to the absence of a primary vagotonic influence, and attested to a decrease in the sensitivity of B-adrenoreceptors. The acceleration of rhythm was also not significant after the administration of ephedrine. The increase in the systolic index in the orthostatic test exceeded the appropriate values by 9.34 percent; in the atropine test by 5.47 percent; ephedrine test, by 2.85 percent. It is known that an increase in this index more than 5 percent over the norm may be one of the signs of defective functioning of the heart muscle or of a disturbance in the sensitivity of its receptors.

The data obtained attest to a significant frequency of dysfunction of the vegetative nervous system in individuals who experienced the influence of small doses of ionizing radiation. The tendency to bradycardia is associated with the secondary predominace of the tonus of the vagus nerve as a consequence of a decrease in the sensitivity of the B-adrenoreceptors.

S. V. Kozin (Moscow)

Hyperthermia as an Element of Polyradiomodification in the Radiation Therapy of Tumors

Hyperthermia (HT) is a most powerful modifier of the radiation therapy of tumors, which, however, is far from having exhausted its potential capabilities. One of the approaches to a further increase in the effectiveness of thermoradiotherapy (TRT) is the additional use of other modifying agents, i. e., the working out of protocols of

polyradiomodification (PRM), one of the elements of which, as a rule, the chief element, is HT.

Today the most effective modifier of TRT is artificial hyperglycemia (AH). In experiments on mice with solid Ehrlich carcinomas, the advisability of the post-radiation sequential use of of AH and HT has been proven, given which it was possible to maximally intensify the antitumor effect of radiation (with a dose change factor of about 3) without change in the radiation reactions of the adjacent skin. The high effectiveness of this protocol of PRM has also been demonstrated in the radiation therapy of mice with melanoma B-16 and Lewis lung carcinoma.

In addition, three other important facts were established in experiments on Ehrlich carcinoma: 1) the effectiveness of the PRM protocol which has been developed increases substantially with in the size of the tumors; 2) AH permits a significant decrease in the thermal load - irradiation with following AH and HT, with heating only to 40°C yielded the same antitumor effect as TRT without AH, but with heating at 45°C; 3) the assessment of the degree inhibition of blood flow in the tumors under the influence of AH and HT can be used for the prediction of the individual effectiveness of these radiomodifying methods.

The therapeutic significance of the suppression of the blood supply of tumors with HT attests to the promise of the development of PRM protocols with the use of vasoactive agents. It has been demonstrated that administration of mexamine to mice before heating additionally increases the effectiveness of TRT, including in the case of its combination with AH.

Under conditions of the combined use of metronidazole and HT with irradiation of Ehrlich carcinomas, it was not possible to obtain a large therapeutic benefit as compared with those achieved with the use of these modifiers separately. The combined use of metronidazole, irradiation, AH, and HT proved to be highly effective.

The assessment of the expediency of combinations of TRT with radioprotectors is of interest. Preliminary results have been obtained regarding the effectiveness of irradiation under conditions of atmospheric hypoxia followed by HT.

K. A. Kosharko, Yu. A. Ippolitov, N. N. Kovtun (Voronezh)

The Influence of Small Doses of β-Radiation on the Mitotic Cycle of Cells of the Mucous Membrane of the Gums in an Experiment

Considerable experience has by now been accumulated with the successful use of radiation therapy in nontumor diseases. However, a certain caution exists in relation to the cancerogenic consequences of radiation therapy, which restrains its use in clinical practice. Therefore the urgency of research directed toward the study of the mechanism of action of small doses of radiation in nontumor diseases remains.

The mitotic cycle of cells of the mucous membrane of the gums of dogs was studied, taking into account the fact that the pathology of mitosis is considered a fundamental feature of tumor growth. The increase in the number of pathological mitoses in the initial stages of the malignant transformation of the epithelium, before the appearance of signs of invasive growth, is a reflection of the process of "cell selection" at the early stages of tumor progression (I. A. Kazantseva, 1981).

The experimental investigations were carried out by means of standard flexible beta applicators with radioactive nuclides, ruthenium-106 + rhodium-106, in 28 dogs. An area of the mucous membrane of the gums was subjected to contact irradiation by the extended fractional dose method in single doses of 0.25 - 0.5 Gy , and total doses of 1 - 10 Gy.

Biopsies of irradiated and non-irradiated areas of the mucous membrane of the gums were performed after the irradiation; cryostatic sections up to 10 — were prepared.

As a results of the analysis of the data obtained, significant differences in the mitotic cycle of cells of the irradiated and non-irradiated areas of the mucous membrane of the gums were not identified over the course of two years following the exposure, which permits the recommendation of these single and total doses for the application of beta therapy of nontumorous diseases of the mucous membranes of oral cavity.

M. N. Kuznetsova (Obninsk)

Experimental Simulation of Acute Radiation Reactions Provoked by Reactor Neutrons

Careful study of the beam parameters in different biological models, determination of the RBE [relative biological effectiveness], and a precise assessment of the degree of injury to normal tissues falling within the field of irradiation are needed for the successful clinical application of neutrons from the BR-10 reactor.

In the present paper, data are presented of a study of early radiation reactions of the skin of rats from a dose (2-8 Gy) of radiation created by neutrons with an average energy of 0.85 MeV.

The preliminarily depilated skin of the the thigh of the animals was subjected to local irradiation in vivo. The RBE of the neutron radiation was determined in comparison groups on the basis of the identical manifestations of the skin reactions relative to irradiation with γ-quanta of ^{60}Co (6-24 Gy).

The development of the radiation reactions was observed regularly and evaluated visually over the course of 40 days. To express the degree of the severity of the acute radiation reactions quantitatively, taking account of the times of the manifestation, a 10 code scale

of estimations was developed, using the recommendations of the WHO and the work of M. S. Bardychev. Depending upon the degree and the area of the injury, a code of 1 - 10, from threshold erythema to extensive ulceration, was assigned. The presence of such factors as edema of the extremity, hematoma, marked epilation, ulceration of the foot, increased the code of the reaction by 0.5 unit. The times of the manifestation of the reaction were taken into account by means of the empirical formula:

$$M = (N - 1)100 + (100 - 2.5n),$$

where M represents the points of the severity of the radiation reactions; N represents the code of the reaction; n represents the days of the observed effect. The analysis of the experimental data using the proposed formula permitted the construction of curves of the time course of the acute radiation reactions of the skin, and in the process, the quantitative estimation not only of the stage of the maximal height of the reaction, but also of the process of healing, as well as of the overall indicator from the beginning of the manifestation of the reaction all the way to the restoration of the hairy integument.

The assessment of the time course of the acute radiation reactions of the rats' skin in the groups following neutron and γ-irradiation permitted the calculation of the RBE of the reactor neutrons on the basis of this criterion. The RBE was 4.2 in the 2 - 8 Gy range of doses for a 50 percent effect. Moreover it was observed that the RBE increase insignificantly with increasing dose.

V. I. Legezeva, M. G. Shagayan (Leningrad)

Neurohumoral Mechanisms of the Primary Reaction to Irradiation

This study was devoted to the investigation of the role of endogenous bioregulators (monoamines, prostaglandins, neuropeptides, etc.) in the pathogenesis of gastrointestinal symtpoms (vomiting and diarrhea) of the primary reaction to irradiation of the organism. The appearance of post-radiation vomiting is governed to a significant extent by stimulation of the chemoreceptor trigger zone (CTZ) of the vomiting center by dopamine, histamine, and opioid peptides released under the influence of the radiation effect; the emetic effect of these is realized through the D^2, H_1, and μ-receptors of the CTZ. Prostaglandins and acetylcholine also play a definite role in the induction of vomiting.

Post-radiation diarrhea is associated with the action of the prostaglandins, histamine, and serotonin released from the mast and endocrine cells of the digestive tract on the intestine; the effects of serotonin are mediated through the D and M type receptors, while that of histamine are mediated through the H_1 and H_2 receptors.

These substances stimulate the secretory and suppress the absorptive function of the intestine, which leads to an increase in its propulsive activity and the development of diarrhea.

The comprehensive employment of pharmaceutical agents which possess pharmacological activity in relation to the different neurochemical structures participating in the regulation of the vomiting reflex and the motoric evacuative function of the intestine is the most promising approach to the treatment of the primary reaction to irradiation. Among these agents are substituted benzamides (metochlopramide, dimetpramide), antihistamine and antiserotonin preparations (peritol, suprastine, cimethidine, dihydroergotamine), inhibitors of prostaglandin synthesis (indomethacin, voltaren), endorphin antagonists (naloxone), and M cholinolytics (methacin).

L. S. Lubotskaya (Leningrad)

Radiation Therapy of the Generalized Forms of Pliss Lymphosarcoma

Malignant tumors of lymphoid origin are often subjected to local radiation therapy, whereas the process is already widely disseminated. In this case, it is important to know, in relation to the strategy of further treatment measures, how the preclinical lymph nodes are reacting to the post-radiation regression of the primary focus. The purpose of the present study was the investigation of the rates of growth of remote lymphogenic metastases against the background of the post-radiation regression of the primary focus, or in the case of its normal proliferation.

Tissues of primary Pliss lymphosarcoma were introduced endolymphatically, inducing numerous foci of tumor growth in the animal's lymphoiod system. The primary focus and regional lymph nodes (popliteal and inguinal) were included in the field of irradiation; the paraaortic, subaxillary, and inguinal lymph nodes of the opposite side were left under the irradiation shield.

The average life span of the irradiated and control animals was identical (on the average 21 +/- 2.1 days). The weight of the tumor on the day of death of the animals was in the 47.3 +/- 8.4 g control and 50.2 +/- 4.4 g in the irradiated animals. However, without irradiation the tumor masses were localized in the region of the primary focus, whereas in the experiment the principal tumor masses were located in the paraaortic, subaxillary, and inguinal lymph nodes of the opposite side which were under the shield at the moment of irradiation. This pattern cannot be associated with the inhibition of the proliferation of lymphogenic metastases of the developing principal tumor, since under conditions of the growth of the nodes from the two primary foci, no competition between them was found under our conditions.

Thus, the stimulation of remote lymphogenic metastases by post-radiation regression of the primary tumor may prove to be a convenient period for systemic prophylactic influences.

P. N. Lyubchenko, E. B. Dubinina (Moscow)

The Enzyme-Producing Function of the Small Intestine in Individuals Who Had Participated in the Elimination of the Consequences of the Accident at the Chernobyl NPP

It is known that disease of the small intestine in the form of diarrhea, sepsis, and endotoxic shock is observed in the presence of the influence of ionizing radiation in large doses (1 Gy and above). The intestinal syndrome is often a cause of death.

The purpose of the present study was the investigation of the activity of the intestinal enzyme β-galactosidase in the presence of the influence of ionizing radiation in small doses in workers who had participated in the elimination of the consequences of the accident at the Chernobyl NPP

The purpose of the present investigation was a study of the changes developing in the organism of individuals subjected to the effect of low levels of radiation during the elimination of the consequences of the accident at the Chernobyl NPP. The determination of sucrose in the blood following an oral load of 50 g of lactose was used to assess the activity of β-galactosidase; concurrently the amount of hydrogen in the expired air was investigated.

Eighty-two men, aged 33.7 +/- 1.6 years, who had received a relatively small dose of external irradiation, namely, 22 rem on the average over the course of two months in 1986 and 9.3 rem over the course of 2.5 months in 1987, were examined.

Selective malabsorption of lactose was found in 48.8 +/- 5.5 percent of the subjects (it was found in 42.8 +/- 8.4 percent of the control; the difference was insignificant). When the two groups were compared (54 individuals who worked at Chernobyl in 1986, and 28 individuals who worked there in 1987), the frequency of hypolactasia was 44.4 +/- 6.8 percent and 57.1 +/- 9.4 percent, respectively. When the hydrogen in the expired air was determined in the process of testing the lactose tolerance, the reverse relationship between the elevated level of sucrose in the blood and the increase in the content of hydrogen in the expired air was observed. The maximal increase in the content of hydrogen in the expired air was observed 1.5 h after ingestion of the lactose.

Thus, the insufficiency of the intestinal enzyme β-galactosidase is not so often encountered in young men who had experienced the influence of ionizing radiation in small doses as it is among the population of the region.

S. V. Martynenko, Yu. A. Grinevich, V. A. Baraboy, E. F. Khinzitskaya (Kiev)

The Endocrine Function of the Thymus in Oncological Patients During Therapeutic Gamma-Neutron Irradiation

Total X-irradiation (4-8 Gy) and neutron (1-2 Gy) irradiation (of 300 rats) leads to a substantial dose-dependant decrease in the level of thymic humoral factor (THF) in the blood, caused by both the direct and mediated (with screening of the thymic region) effect of radiation on the thymus.

Taking the possible mediated effect of radiation into account, the content of THF in 72 patients with tumors of the locomotor apparatus (TLA) and the head and neck region in the process of gama and neutron therapy was studied. At the same time the content of E-RFC, E_M-RFC, immune complexes (IC) and class A, M, and G immunoglobulins (Ig) was determined.

The preoperative neutron irradiation of patients in a dose 4 - 8 Gy, while insignificantly elevating the level of immune complexes and IgA and G, leads to a marked suppression of the endocrine function of the thymus ($\log_2$ of the THF titer decreased from 3.52 +/- 0.20 to 2.22 +/-0.24 in patients with TLA and from 3.16 +/- 0.19 to 2.0 +/- 0.20 in patients with tumors the head and neck. Neutron irradiation following a radical protocol (11.8-14 Gy) of patients with TLA makes the changes in the immune system observed after preoperative irradiation more profound. A further decrease in the level of THF in the blood serum to 1.92 +/- 0.26, an increase in the Ig content (by a factor of 1.74) and IC (by a factor of 1.54) in relation to the initial level are also noted.

Thus, radiation therapy, especially following a radical protocol, substantially decreases the content of thymic hormones in the circulation, which indicates the advisability of the utilization of thymic preparations in the comprehensive therapy of malignant neoplasms. According to preliminary data, the utilization of Tactivin (100 μg per dose intramuscularly every 48 h starting with the second half of the course of radiation therapy) against the background of a marked decrease in thymic hormones normalizes the level of THF and IC in the blood.

L. I. Masarskiy (Leningrad)

On the Choice of the Physico-Technical Characteristics of a Model of Radiation Effect in a Radiobiological Experiment

In the setting up of radiobiological experiments on the simulation of radiation effects on man, the attempt to achieve dosimetric similarity of the conditions of the irradiation of experimental animals to the conditions of the irradiation of people in the modeled radiation situations.

The contemporary level of the development of the techniques and methods of dosimetry, as well as of computer technology, permit the assessment of the distribution of doses throughout the human body quite objectively and informatively, in the majority of practical instances of its external irradiation.

This provides a basis for large degree of specification of the dosimetric parameters in the choice of a model of radiation effect in a radiobiological experiment, which, however, has practically not been done up to the present time. Certainly, the specification of the dosimetric

parameters of a model of radiation effect in a radiobiological experiment on the basis of an analysis of the dosimetric characteristics of the conditions of the irradiation of a human being in the modeled situation may permit the more objective assessment of the predictive capacities of the results obtained. However, to achieve the expected effect from such a specification it is necessary to achieve a unified interpretation of the concept of "dosimetric similitude" itself.

In view of the subtantial difference in the character of the radiation injury to the organism in acute and chronic radiation effects, the criteria of dosimetric similitude for these two principal groups of models of radiation effect must be distinguished.

On the basis of knowledge of contemporary biological notions regarding the processes of radiation injury of the organism, it seems expedient to choose the equivalence of the dosimetric spectra with respect to red bone marrow and intestinal (the principal critical systems for the development of the syndromes of acute radiation illness) weights as the criterion of dosimetric similitude in the case of acute radiation effects, and in the case of chronic radiation effects, the equivalence of the average doses absorbed in the bone marrow.

E. Yu. Maslov, A. V. Budlyanskiy, T. Yu. Kuznetsova (Sverdlovsk)

Hyperglycemia - Radiosensitization or Radioprotection

Experimental and clinical investigations of recent years convincingly attest to the possibility of the utilization of local or general induced hyperglycemia as a factor selectively influencing radiation damage to tumors. The mechanism of this phenomenon has been explained by the dependance of the radiation effects on the level of lactate forming in the tumor.

The radioprotective effect of hyperglycemia is less well studied.

The purpose of the present study was the assessment of the radiomodifying properties of glucose in an experiment on BALB mice weighing 20 g during total γ-irradiation in doses of 7 and 8 Gy.

The dose-regulated hyperglycemia was created by means of the intraperitoneal administration to the animals of a 40 percent solution of glucose in a quantity of 100-400 mg per mouse at different time intervals before and after irradiation. In addition to the intact mice, a series of parallel experiments was run in animals with transplanted sarcoma 37. The effectiveness of the radioprotective properties of glucose was assessed on the basis of the periods of survival of the experimental and control groups of animals, kept in identical conditions.

The results of the experiments permit the following preliminary inferences to be drawn:

1. The intraperitoneal administration to the animals of glucose in doses of 100-300 mg per mouse does not influence the life span of the irradiated animals, and at a dose of 8 Gy it leads to its shortening.

2. When glucose is administered in a dose of 400 mg per mouse, the life span of the animals with irradiation at a dose of 7 Gy increases.

3. The tumor-bearing animals were more sensitive to the effect of the radiation; however, in these groups a pronounced radioprotective effect of the glucose is observed when it is administered in a dose of not less than 400 mg per mouse.

I. N. Morozova, S. N. Lebedev (Leningrad)

The Influence of Cystamine on Some Indicators of the Immunological Reactivity of the Irradiated Organism

Injury of the genetic apparatus of immunocompetent cells may be one of the possible causes of post-radiation immunodepression.

The purpose of the present study was the investigation of the of the modifying effect of cystamine on the post-radiation disruption of the structure of DNA of blood lymphocytes and the number of antibody-forming cells and B-lymphocytes in the spleen.

The experiments were carried out in white male mongrel mice, subjected to irradiation in a dose of 4 and 6.5 Gy, at a dose rate of 1.9 Gy/min. The cystamine was administered intraperitoneally in a dose of 150 mg/kg (with respect to the base) 15 min prior to the radiation effect.

Irradiation in a dose of 4 Gy elicits a decrease in the number of B-lymphocytes on the average by a factor of 10, while in the protected animals it exceeds their values in the irradiation control by a factor of 6. At a dose of 6.5 Gy the number of antibody-forming cells in the spleen decreases significantly (by 2 orders of magnitude) as compared with the initial level, while under the influence of cystamine the number of these cells is found to be 5 times greater. The investigation of the impairment of the genetic apparatus showed that 5 min after the irradiation the number of single-stranded DNA breaks (ssb DNA) in the lymphocytes increases on the average up to 2.7 per 2.3×10^9 dalton fragment. By the end of the first day the number of post-reparative ssb DNA reaches the level of 2.3 breaks per fragment. In the cystamine-protected animals, the number of primary and secondary ssb DNA was lower by a factor of 2-3 on the average than in the irradiated control.

Thus, cystamine, by protecting the genetic apparatus of the lymphocytes, promotes the preservation of a larger number of functionally active immunocompetent cells.

G. S. Mushkacheva, G. G. Rusinova, K. N. Muksinova, V. K. Lemberg, V. B. Shorokhova, V. S. Revina, T. I. Uryadnitskaya (Moscow)

Damage to the Genetic Structures of Cells and the Remote Effects of Prolonged Irradiation

The high degree of radiosensitivity of genetic structures and their unique role in the life of the cell determine the paramount significance of damage to these structures in the formation of both immediate and remote consequences of a radiation effect. In this paper we have correlated the results of a many year long experimental study of the genetic structures of somatic cells during a long-term radiation effect. Dose-dependant injuries of the higher levels of organization of nuclear DNA and its primary and secondary structure, as well as of the processes of repair, replication, and transcription, have been identified. These molecular changes are realized at the subcellular level in chromosomal rearrangements. The frequency of these rearrangements and their severity, the formation of rearrangements which are specific for malignant transformation, as well as of clones of cells with atypical chromosomes depended on the dose rate and total dose.

Data on the genotoxic effect are compared with the remote effects and are discussed in the light of contemporary notions regarding the role of damage to hereditary structures in cancerogenesis.

O. K. Nayanova

The Radiomodifying Effect of an Electromagnetic Field in the Acoustic Range

Mongrel rats with an S-45 solid tumor transplanted subcutaneously into the right thigh served as the object of these investigations. The temperature of the tumor and of the normal muscle tissue, the volume of the tumor, and the average life span of the animals, served as the criteria of the effect. All of the criteria were studied in the same time periods.

All of the animals were divided into two groups. Thirty animals, in which the temperature and volume indices were studied during and after the irradiation of the tumor, were included in the first group. The second group was made up of 40 animals in which the dynamics of the temperature and the volume indices were assessed in the case of irradiation of the tumor with preliminary placement of these animals in an EMF.

The influence on the tumor-bearing organism of the ionizing radiation and an EMF in the acoustic range were begun from the twelfth day following the transplantation of the tumor, when its volume reached 6 - 7 cm^3.

As the investigations showed, the temperature reaction of the normal muscle tissue and of the tumor to preliminary total exposure to an EMF in the acoustic range is different. It is acccompanied by the alternation of hyper- and hypothermia in these tissues, which are manifested in opposing phases.

This makes it possible to use an EMF in the acoustic range during the irradiation of a tumor as a radiomodifier, and to increase the effectiveness radiation therapy of tumors with simultaneous protection of the surrounding normal tissues.

R. V. Petrov, I. V. Oradovskaya, V. P. Pinegin, I. V. Fadeyeva, V. D. Prokopenko, L. V. Luss, T. A. Chervinskaya, V. N. Androsov (Moscow)

The Clinical Immunological and Allergological Characteristics of Individuals Who Had Participated in the Elimination of the Consequences of the Accident at the Chernobyl NPP, 3 Years After Leaving the Zone of the Accident Restoration Operations

In the program of tracking of the state of health and immune status of the contingent of individuals who had participated in the elimination of the consequences of the accident at the Chernobyl NPP, 836 individuals were examined after three years. Positive dynamics were identified in the clinical immunological examination as compared with the preceding examination, which is expressed in a decrease in the number of individuals with clinical manifestations of immunological deficiency: those frequently ill with AVRI [acute viral respiratory infections] (6.34 percent $<$ 11.44 percent), and those frequently ill with secondary bacterial infections of the skin and subcutaneous fat (1.44 percent $<$ 2.05 percent). A decrease in the frequency of occurrence of the "syndrome of increased fatigability" (24.52 percent), which was quite frequently recorded (41.60 percent) in the initial years of the examination, and neurocirculatory dystonia (5.36 percent $<$ 8.92 percent) were also noted.

The clinical allergological examination was carried out in 224 individuals living in one of the cities of Leningrad Oblast; a positive history for allergy was noted in eight individuals (3.5 percent). Positive skin tests with atopic allergens were identified in five individuals (2.2 percent). There were clinical features of the presence of allergic diseases in all five individuals with positive skin tests: pollinosis of the rhinoconjunctival form in four individuals; the rhinitis of allergy to dust in one individual, which coincided completely with the allergy history. Changes in the values of the external respiratory function (ERF) were not observed in any of the five individuals with allergic diseases. When the values of the ERF were analyzed, it was established that deviations were not identified in the ERF values in 117 (60.3 percent) out of 194 subjects. Changes in the values of the external respiratory function of the obstructive type of the first degree were observed in 22.2 percent (43/194), of the restrictive type of the 0-1 degree were observed in 14.4 percent (28/194), of the mixed type were observed in 3.1 percent (6/194). It should be noted that more than 90 percent of the workers with changes in the ERF are smokers.

Thus, judging from the results of the clinical allergological examination, the level of morbidity from allergic diseases in the contingent examined (2.4 percent) were

not higher, and were even lower as compared with the similar parameter in other cities of the Leningrad region, for whom, according to the data of G. B. Fedoseyev and co-authors (1981), it is equal to 5 - 10 percent.

Positive dynamics have been observed in the indices of immune status.

G. V. Plaksina, S. A. Yakovlev, L. I. Antoshina (Moscow)

A Crystallographic Investigation of the Blood Serum of Individuals Who Had Participated in the Liquidation of the Accident at the Chernobyl NPP

Crystallographic methods, based on the fact that the character of the crystallization of biological substrates depends mainly on the properties of the protein gel, have been used successfully in recent years in practical medicine. The structure and density of the gel, the amino acid composition of the proteins, and the conformational changes of protein compounds also exert an influence on the growth of crystals.

Methods of the study of solid crystal texture using an alcoholic solution of $CuCl_2$, ninhydrin, and the crystallography of the native substrate based on a modified methodology which achieves a slowed course of the mesophase of crystallization have been employed. This significantly extends the information regarding the anisotropy of the physical parameters of the forming textures. The results are assessed using light and polarizing light microscopy.

Forty-two individuals (of these 38 were men), aged 20 - 45 years, who had received a dose of external ionizing radiation up to 25 rem, were under observation.

Changes in the configuration of the structures in the form of needle-shaped fragments of rays and of frequently intersecting, short bundles with bright luminosity, were identified in the crystallograms of blood serum with $CuCl_2$ in two-thirds of the subjects. Such a pattern in the crystallograms correlated with the presence in these individuals of gastroenterological pathology.

Crystallography of the native serum with a slowed crystallization process made possible the identification in one-third of the subjects, in addition to an increase in the morphological types of crystals, pathological anisotropic textures in the stratified-dendritic and other forms. The observed changes were not noted in the control group, which makes possible the use of this test as one of the criteria for the identification of a risk group, individuals who are to be subjected to additional clinical laboratory investigation.

S. A. Prosvernitsyn, Z. Yu. Shchurigina, A. E. Antushevich, A. E. Egorov (Leningrad)

The Structural-Biochemical Bases of Post-Radiational Cerebral Edema

The elucidation of the pathogenesis of the cerebral form of acute radiation illness has been made significantly more difficult because of the controversial character of the information regarding the origin of so severe a manifestation of it as cerebral edema. The purpose of this investigation was the determination of the possible mechanisms of the development of early post-radiational cerebral edema. The experiments were set up in guinea pigs and white rats subjected to irradiation in doses of 100 and 150 Gy, respectively.

It was established through the use of ^{14}C-urea that the permeability of the blood-brain barrier (BBB) is decreased following irradiation.

When the permeability of the BBB for colloidal lanthanum was investigated electron microscopically, the penetration of the latter beyond the limits of the endothelium of the capillaries was also not detected 0.5-2 h following irradiation. The morphological features of edema and swelling were clearly identified 1 h following irradiation in the cytoplasm of the granular cells of the cerebellum, and less markedly in the neocortex. Subsequently (by 2 h), the volume of the edema-altered areas in the cerebellum increased up to 12 - 15 percent.

The edematous changes were observed in animals which had been subjected to direct irradiation of the head; the edema was insignificantly expressed when it was screened.

Biochemical investigations made possible the identification of a decrease in the activity of prekallikrein by 20 percent 15 min after the effect and by 50 percent 60 min after the effect.

The advance development of edema in nerve cells, the preservation of the intercellular spaces and elements of the BBB, the decrease in the permeability to ^{14}C-urea, and its absence for lanthanum, as well as the activation of the kallikrein-kinin system make it possible to hypothesize a cytotoxic genesis of the edema observed in the early periods following irradiation, and its development as a consequence of the insufficient activity of the elimination of fluid from the nerve cells through the astrocytes and the BBB.

N. S. Sergeyeva, V. I. Chissov (Moscow)

The Clinical Testing and Approval of Clinical Laboratory Methods of the Individual Predicting of the Reaction of Human Tumors to Radiation Therapy

A correlation has been established in a number of investigations between a change in the proliferative status of tumors during irradiation and their radiosensitivity. These results, which were obtained by the method of autoradiography, have served as the basis for the development and application in clinical practice of rapid methods for the determination of the proliferative

activity, and for the study of the poss of using them for the prospective forecasting of the individual reaction of tumors to irradiation.

The proliferative activity (the proportion of cells in the S phase of the cell cycle) of solid human tumors (cancer of the oropharyngeal zone, of the esophagus, stomach, rectum, and lung; 400 cases in all; of these 120 were in the process of radiation therapy) were assessed in the present study by the direct immunofluorescent method, using antithymidine antibodies. The proliferative activity of the tumors varied within the limits of a group of patients that was uniform with respect to clinical and histological parameters. The level of the initial proliferative activity cannot be used for the individual forecasting of the clinical reaction of the tumor to irradiation. At the same time, the change in the proliferative activity of the tumor at the beginning of the course of radiation therapy (following the application of a dose of 12 Gy) in 87 percent permits the prediction of the reaction of the primary tumor node (the degree of resorption and/or the degree of radiation injury to the tumor tissue) to the the next course of irradiation.

The data obtained attest to the real possibility of the utilization of rapid methods of determining proliferative activity for the prospective forecasting of the radiation reaction of tumors in individual patients.

R. V. Smirnov, R. A. Aleksandrova (Petrozavodsk)

The Expressivity of the Injurious Action of Ionizing Radiation on Tumor Cells as a Function of the Duration of Their Mitotic Cycle

Tumor cells of epithelial origin, namely, CHO-K1 (length of mitotic cycle 14 h), HeLa (20-21 h), and PPM (44 h) were used. The cells were grown in Carel flasks; the Puck-Marcus method was accepted as the basis for the determination of the survival rate of the cells.

The irradiation was carried out on the fifth day following seeding (the stage of stationary growth) in doses of 1, 2, or 4 Gy, using an RUM-17 apparatus at an X-ray tube voltage of 2 kV. The seeding of the cells (1,000 cells) after exposure was made to solid nutrient medium after 1, 24, or 48 h in five flasks. The seeding of nonirradiated cells was carried out concurrently as the control. The colonies were fixed on the eighth to tenth days a mixture of ethanol and glacial acetic acid in a ratio of 3:1; they were stained with hemalum and counted. The survival rate of the cells was defined as the ratio of the number of colonies grown from the irradiated cells to their number in the control.

An increase was observed in the injurious effect of irradiation at a dose of 1 Gy in the case of seeding after 1 h in the following order: CHO-K1, HeLa, PPM. Analysis of the data obtained indicates that an increase is observed in the survival rate of the cells with increase in the time of seeding after irradiation. The radiosensitivity increased after seeding after 24 or 48 h in the following order: CHO-K1, PPM, HeLa.

The results of the experiments indicate that the rate of repair of the radiation injury when the cells are seeded in the phase of division delay (seeding 1 h after irradiation) is in inverse relationship to the length of their mitotic cycle. When the cells are seeded at later periods (24, 48 h), this regularity is not maintained.

R. V. Smirnov, O. V. Smirnovova (Petrozavodsk)

The Influence of the Sequence of Exposure to X-Ray Radiation and Ultrasound on the Antitumor Effect in an Experiment

The experiments were set up in 180 mongrel sexually mature male mice: the first group was the control; the second group, the effect of X-radiation (XR) on the solid Ehrlich carcinoma in a dose of 5.6 Gy; the third group, the effect on the tumor of ultrasound for 5 min at an intensity of 2 Wt/cm^2; the fourth, the combined effect at the same doses in the XR + ultrasound sequence; the fifth, the combined effect in the ultrasound + XR sequence.

The control and the experimental animals were anesthetized after 3, 6, 9, 15, 24, 48, or 72 h. The injurious effect of the irradiation was assessed on the basis of the mitotic index (MI) and the frequency of pathological mitoses (PM), as well as their spectra.

A brief suppression of mitotic activity was observed in the irradiated mice, the degree of which increased in the following sequence: the third, second, fourth, and fifth group. The MI began to increase after 6 h in all the irradiated mice, and then it recovered to the initial values: in the fourth after 24 h; in the second group and the third group, in the course of the second day; and in the fifth group, after 48 h.

The frequency of PM in the animals of the control group was 5.4 percent (classification of I. A. Alov). Their spectrum was characterized in the following manner: multipole mitoses, 35.3 percent; multigroup metaphases, 11.8 percent; separation of chromosomes, 17.6 percent; and adhesion of chromosomes, 5.9 percent. The pathological mitoses associated with injury to chromosomes were 53 percent; those associated with injury to the mitotic apparatus, 43 percent.

The frequency of PM increased in the first 6 h in all the exposed animals: the second group, 33.3 percent; the third group, 10 percent; the fourth group, 50 percent; the fifth group, 50 percent. A second significant increase in the frequency of PM was observed in the second group after 15 h and in the third group after 72 h. The spectrum of the PM changed in the second group as the result of the appearance of hollow metaphases, in the third of asymmetric mitoses and hollow metaphases, and in the fifth, asymmetric mitoses and pulverization of chromosomes. The frequency of PM associated with injury to chromosomal apparatus increased in the fifth group up to 78 percent as compared with the control.

The results of these experiments indicate that the more pronounced injurious effect of combined irradiation was observed with the ultrasound + XR sequence, in which the biological effect exceeds the simple summation of the injuries induced by the agents employed.

Yu. E Strelnikov (Leningrad)

The Mechanism of the Antiradiation Action of Radioprotectors

In investigating the mechanism of the action of radioprotectors, we have proceeded from the univerality of the oxygen effect and the need to protect the critical target in the cell, DNA.

Thirty of the most effective radioprotectors from different classes of chemical substances (aminothiols and their disulfides, cyclic sulfur and nitrogen-containing compounds, adrenomimetics, indolylalkylamines, anticholinesterase agents, thiopyrimidines, methemoglobin-forming compounds, lipopolysaccharides, cytostatic agents, etc.) were utilized.

The most characteristic properties of the radioprotectors, irrespective of their structure, is the suppression of oxidative processes. This is expressed in a decrease in the consumption of oxygen and an increase in survival in an enclosed space, and in the inhibition of the oxidation of hexenal in the liver, which is accompanied by a decrease in body temperature. The capacity of various radioprotectors to prevent the death of animals from the toxic effect of oxygen under increased pressure and to attenuate the intoxication by various substances, the toxicity of which is governed by their oxidation products in the organism, is probably associated with the suppression of oxidative processes. The suppression of oxidative processes is accompanied by hypoxia, which is indicated by a decrease in oxygen tension in various organs, by shifts in the acid-base status due to an increase in the amount of unoxidized products of metabolism, lactate and pyruvate, as well as by the weakening of adaptive gas exchange in response to the cooling of animals. The temporary suppression of DNA synthesis in radiosensitive organs is an obligatory manifestation of the radioprotective effect of the traditional radioprotectors. A definite link has not been identified between radioprotective activity and the capacity of radioprotectors to change the level of one cyclic nucleotide or another, or their ratio.

R. S. Tishenina, D. S. Valiulina (Moscow)

The Processes of Free Radical Lipid Oxidation in Individuals Who Had Participated in the Liquidation of the Accident at the Chernobyl NPP

One of the early effects of the irradiation of man is the pathological activation of the processes of the free radical oxidation (FRO) of lipids. Since it was practically impossible to assess the processes of the intensification of the FRO of lipids when people were still in the zone of the accident at the Chernobyl NPP, it was of interest to study the FRO of lipids in individuals who had participated in the liquidation of the accident, after they had left the zone of the elevated radioactive background. Fifty-two such individuals were studied in 1986, and 49 in 1987.

The concentrations of hydroperoxides of the lipids and malondialdehyde (MDA) in the plasma and erythrocytes, which reflect the state of the processes of the FRO of lipids were higher in 1986 than in 1987. The intensification of the FRO of lipids proceeded against the background of an increased total plasma lipid content, and, which is especially important, against the background of an increased concentration in the plasma and erythrocytes of one of the powerful antioxidants, α-tocopherol. Normalization of the level of MDA and of α-tocopherol was established in the erythrocytes in the individuals examined in 1987. It is very important that the content of cholesterol in the erythrocytes and the index of antioxidant deficiency in individuals with excessive activation of the FRO of lipids did not differ substantially from the corresponding indices in the healthy individuals.

The characteristics of the FRO of lipids and the hormonal homeostasis have been investigated in individuals in whom enlargement of the thyroid gland had been identified after they had been in the zone of the accident at the Chernobyl NPP.

L. N. Ulyanenko (Obninsk)

Early Postradiation Changes in Enzymatic Activity of the Blood of Farm Animals

A study of the dynamics of the activity of enzymes participating in energy exchange, and of transamination enzymes in various species of farm animals with external total γ-irradiation (^{137}Cs) enabled us to identify both general patterns and species-specificity. A significant increase in the activity of lactate dehydrogenase (LDH) in the blood plasma of irradiated (0.085 C/kg) sheep on the third to seventh day after exposure, as well as an insignificant increase in the activity of creatine phosphokinase and hydroxybutyrate dehydrogenase (HBD), were noted. The same tendencies to a change in the postradiation dynamics of the activity of the enzymes under investigation were also characteristic of horses. Probably such activation of the enzymatic activity, especially in the early post-irradiation periods, can lead to intensification of the processes of carbohydrate metabolism. In addition to this, a substantial ($p < 0.05$) decrease in the activity of aspartate aminotransferase (AAT), and a marked two-fold decrease in the activity of glutamine aminotransferase (GAT) were demonstrated in the same periods of observation. An increase in the dose of radiation, on the other hand, led to suppression of the activity of blood dehydrogenases with varied expressivity in relation to the periods of the investigation. Thus, a decrease in the activity of HBD was observed in the blood of pigs from the third day of irradiation all the way to the end of the observation (over

the course of 1 month), while the maximal decrease in the level of LDH activity (in individual cases 3 times lower than control values) was found in the blood of horses. The CPK activity in the blood plasma of sheep decreased more than 50 percent in the early post-irradiation periods. At the same time, the given increase in the radiation dose did not induce significant changes in GAT activity. A brief decrease in AAT (on the fifth day of the investigation) and alanine aminotransferase was detected in the blood of sheep.

S. E. Ulyanenko (Obninsk)

The Features of the Radiomodifying Effect of Induced Hyperglycemia

This study is devoted to an analysis of some features of the effect of brief hyperglycemia, features which emphasize its significance and place as an adjuvant in the multifactorial therapy of malignant neoplasms.

Along with the well-known phenomena of hyperglycemia, the metabolic decrease in pH and the disturbance of the microcirculation in tumor tissues, we direct attention to the importance of the investigation of the biochemical processes of glycolysis for the understanding of the mechanism of radiomodification. The data obtained on the varying degree of the intensification of the hyperglycemia-induced vulnerability of some tumors to ionizing radiations of varied LET [linear energy transfer] (γ-quanta and fast-neutrons) make it possible to draw a conclusion regarding the synergism of the interaction of hyperglycemia and the radiation effect.

In multifactorial therapy, which also includes chemotherapeutic preparations of different classes, hyperglycemia should also be regarded as an agent which substantially alters the pharamcokinetics of these preparations. A significant increase has been demonstrated in the tropism of bleomycetin for tumor tissue under hyperglycemic conditions.

N. G. Chigareva (Leningrad)

The Effectiveness of Indomethacin in Minimal Absolutely Lethal Irradiation

Data have been obtained in recent years on the antiradiation protection and therapeutic effect of nonsteroidal anti-inflammatory agents, classified as prostaglandin synthesis inhibitors, in particular, voltaren and indomethacin. Their effect has been established in conditions of total or fractionated irradiation in sublethal doses; however, the possibility and the advisability of their application in absolutely lethal doses are still unelucidated.

The objective of the present investigation was the study of the protective and therapeutic properties of indomethacin, a prostaglandin biosynthesis inhibitor in conditions of total lethal irradiation.

The experiments were set up in white mongrel male rats, body weight 18-20 g. The animals were irradiated at a dose of 7.5 Gy by means of an IGUR unit ($LD_{95\text{-}100/30}$) at a dose rate of 1.62 Gy/min. The indomethacin was administered to the animals in a dose of 2.5 mg/kg in physiological solution by mouth 1 h before irradiation or in a dose of 0.1 or 1 mg/kg subcutaneously 6 h after irradiation and daily over the course of 5 days.

The prophylactic administration of indomethacin had practically no effect on the survival of the animals irradiated at a minimal absolutely lethal dose, although an insignificant increase in the average life span was noted in the experimental group of animals.

The utilization of indomethacin as a therapeutic agent also did not affect the survival of the irradiated mice. However, an acceleration of the restoration of hematopoiesis was detected as compared with the control irradiated animals, indicated by an increase in the myelocaryocyte count in the bone marrow and the number of CFU_s on the seventh to eighth day of the radiation illness.

Possibly the effect of indomethacin is associated with an influence on the migration of bone marrow cells or an increase in their proliferation. An effect of the preparation on the formation of the $\cdot O_2$ superoxide radical and the immune properties of the blood-forming cells, the neutrophils in particular, cannot be excluded. The advisability of the use of the preparation in the complex of treatment methods of acute radiation illness is discussed.

N. N. Shatinina, A. N. Shutko (Leningrad)

The Inhibitory Effect of Total Body Radiation in a Nontumoricidal Dose on the Growth of the Experimental Mouse Bronchial Adenocarcinoma RL-67

The experiments were carried out on male mouse F_1(CBA X C57B1/6) hybrids, with radioresistant bronchial adenocarcinoma RL-67 transplanted under the skin of the foot of the hind paw. The development of the process was monitored, by weighing the tumor mass and calculating the nucleated elements of the myeloid tissue and the formed elements of the peripheral blood in the animals at different times following the transplantation. The radiation (RUM-17; 0.5 Cu+1 mm Al; FSD 96 cm; 0.94 Gy/min) inhibition of hematopoiesis, the degree of which varied, was carried out in the logarithmic phase of tumor development, using total body irradiation (TBI), in a dose of 6.5 Gy, or subtotal body irradiation (STBI) in doses of 6.5, 6, and 4 Gy; in the process the healthy paw was screened, with preservation of approximately 5, 22, and 22 percent of the bone marrow, respectively.

Both types of exposure slowed the rate of increase of the biomass of the tumor proportionately to the degree of suppression of hematopoiesis, based on the indices of the peripheral blood and the bone marrow. In the case of TBI, the total weight of the tumor was less than the control by a factor of 3.7, while in the case of STBI (5 percent screening of the bone marrow) at the same dose, it was less by a factor of 2 on the eleventh day following the exposure. Local irradiation of the tumor at a dose of

6.5 Gy did not lead by the time indicated to significant changes in the weight of the neoplasm.

The effects of the slowing of tumor growth obtained at 22 percent screening of the bone marrow were found to be identical at doses of 6 and 4 Gy, which attests to the presence of an upper threshold dose of 4 Gy for the reproduction of the phenomenon.

V. V. Shikhodyrov, N. N. Klemparskaya, E. P. Somova, V. B. Emelyanov, A. A. Ivanov, G. A. Shalnova (Moscow)

The Characteristics of the Combined Action of γ-Quanta and UHF Radiation

The combined local effect of ionizing radiation and UHF radiation has found broad application in the treatment of oncological patients. In this case, the intensification of the selective antitumor effect of the radiation therapy is the main thing.

In experimental investigations studying the influence of UHF radiation on the living organism, many features have been identied in the changes in immunological reactivity which are common to phenomena which appear in the conditions of injury caused by ionizing radiation. In both types of influences the level of antitissue antibodies in the blood increases significantly, the immune response to foreign antigens is suppressed, the mitotic activity of cells is suppressed, and the permeability of their membranes increases.

When the extensive areas of application of UHF radiations are taken into account, the importance is seen of the investigation not only of mutual intensification of injurious influence, but of the identification of the possibility of the reverse effect as well, i. e., of mutual attenuation.

In experiments on male mice, (CBA X C57B1/6) first generation hybrids, weighing 15-18 g, we studied different types of combination of the influence of UHF radiation and the influence of γ-quanta in doses of 7.5 - 8 Gy at a dose rate of 1.7 Gy/min.

The total influence of the UHF radiation (energy fluence rate [PPE] from 100 to 800 mWt/cm^2, λ = 16 cm, pulse duration 5 μsec, pulse repetition frequency 200 Hz) aggravates the course of the subsequent γ-irradiation. However, the reaction to UHF radiation changes markedly if intact mice are not used, but mice subjected to γ-irradiation; in certain conditions the lethality decreases almost four-fold.

T. M. Yurina, V. N. Shabalin (Moscow)

The State of Some Parameters for the Immune System in Individuals Who Had Participated in the Elimination of the Consequences of the Accident at the Chernobyl NPP

The purpose of this study was the investigation of the state of the immune system in workers who had participated in the elimination of the consequences of the accident at the Cherbobyl NPP in 1986-1987. We examined 104 individuals, of whom 96 were men and eight were women; the average age of the subjects was 33 years.

The total T-lymphocyte population and the T-active subpopulation of RFC were investigated using the sheep erythrocyte rosette method; the phagocytic activity of the neutrophils was studied by the latex particle ingestion method, the serum immunoglobulin content by the Mancini method, and the circulating immune complexes as described by V. Gashkova; the antibodies to DNA were also determined.

The data were analyzed using variation statistics, and were subjected to individual analysis, depending upon the presence of disease, the dose of irradiation received, and the time spent at Chernobyl.

Clinical manifestations of immune deficiency were not observed. Acute or chronic inflammatory diseases were not identified. Hashimoto's autoimmune thyroiditis was diagnosed in four individuals; lesions of digestive organs (chronic gastritis, duodenitis) and disturbances of vegetative regulation were observed in a number of individuals.

The most marked changes were observed in the phagocytic activity of the neutrophils; the level of T-active RFC increased significantly, in the presence of some decrease in total T-RFC. An increase in the level of class G and M serum immunoglobulins took place in one-third of subjects.

The level of antibodies to native and denatured DNA did not exceed the norm.

The data of the investigations attest to some changes in the immune status of individuals who had contact with small doses of ionizing radiation, which necesitates the continuation of systematic observation of them.

IS Elements and Calcium-Independent Yersinia Pestis Mutants

917C0200A Moscow GENETIKA in Russian Vol 26 No 10, Oct 90 (manuscript received 25 Jul 89) pp 1740-1748

[Article by A. A. Filippov, P. N. Oleynikov, A. V. Drozdov and O. A. Protsenko, All-Union Scientific Research "Mikrob" Antiplague Institute, Saratov]

UDC 616.981.452:575

[Abstract] A comparative rstriction analysis was conducted on calcium-independent Y. pestis mutants EV and 358 to evaluate the significance of IS elements in these forms of mutation in strains bearing a single 45-47 MDa pCad plasmid. In the case of Y. pestis EV the plasmid was found to bear the IS100 element at three different sites within the calcium-dependence region. Concomitantly, pCad was also shown to have sustained two extended deletions (ca. 24 kbp) encompassing the entire cad region and representing about two-thirds of the plasmid DNA. Possibly, the deletions were induced by the IS100 element which was shown to lack a HindIII target site. Studies on Y. pestis 358 revealed a novel IS element designated IS101 which was smaller than IS100, possessed a HindIII site, and appeared to be inserted outside the calcium-dependenc region, with the Cad$^-$ phenotype evidently due to the polar effect of its insertion. Finally, IS101 differed from IS100 by high specificity of insertion that was limited to 3 specific sites in the pCad DNA. Figures 5; references 24: 7 Russian, 17 Western.

Hemophilia A Carrier Detection by PCR Analysis of HindIII Polymorphism of Factor VIII Gene

917C0200B Moscow GENETIKA in Russian Vol 26 No 10, Oct 90 (manuscript received 22 Nov 89) pp 1840-1846

[Article by V. L. Surin, M. V. Aseyev, Ye. L. Zhukova, V. S. Baranov, G. Ya. Solovyev, N. I. Grineva, T. A. Andreyeva, V. L. Izhevskaya, Ye. A. Likhacheva and O. P. Plyushch, All-Union Hematological Scientific Center, Moscow; Institute of Obstetrics and Gynecology, USSR Academy of Medical Sciences, Leningrad]

UDC 575:591

[Abstract] Hemophilia A carrier detection was carried out on 62 families in Moscow and Leningrad with a familial history of the disease, employing PCR amplification for demonstration of HindIII polymorphism in factor VIII gene. Amplification and analysis of the intron of factor VIII gene showed that the frequency of polymorphic HindIII sites in 207 unrelated X-chromosomes was 0.29, i.e., 59 unrelated X-chromosomes were affected. According to the Hardy-Weinberg equilibrium the data indicated that the frequency of females heterozygotic for HindIII polymorphism was 0.41 (or 36.5 percent). The corresponding familial carrier rate was shown to be 37 percent, i.e., 23 out of the 62 families were affected. Consequently, PCR-based analysis of factor VIII gene polymorphism appears to offer a reliable method for carrier detection and prenatal diagnosis. Figures 3; references 17: 1 Russian, 16 Western.

Diagnostic Immune Blot Assay for Demonstration of Antibodies to HIV Using a Polyacrylamide Gel Gradient

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[Article by S. S. Marennikova, G. R. Matsevich, E. M. Shelukhina, A. Yu. Sazykin, I. A. Okunev, M. N. Nosik, and L. G. Stepanova, Scientific Research Institute of Viral Preparations, USSR Academy of Medical Sciences, Moscow]

UDC 616.153.962.4-097:578.828.6]-078.3

[Text] Demonstration of antibodies to human immunodeficiency virus (HIV) is the most important criterion for the diagnosis of HIV infection and AIDS. At the present time, immunoenzyme analysis (IEA) is used the most often. However, even repeated use of this test does not rule out entirely the possibility of false-positive reactions, so that final verification is made using the immune blot assays [10]. At the same time, as shown by experience, use of immune blot assays does not always yield an unequivocal answer. There is no difficulty in making a diagnosis when antibodies to the set of main HIV antigens (env, gag, pol) are present in the tested serum. When there is a limited number of bands, there are differences in assessing their diagnostic value. In particular, there is even ambiguity in the opinion about the required number of bands with env-antigens for a positive response. According to the specifications formulated by WHO experts in December 1987, presence of antibodies to any gag or pol protein and to one of the env proteins is a seropositive sign. In the absence of antibodies to gag and pol antigens, there must be at least two bands for env proteins [15]. The American Center for Disease Control considers serum to be seropositive when there are antibodies to any two of the three antigens (p24, gp41, and gp120/160). At the same time, according to the instructions for using the immune blot test system of the Pasteur Diagnostic Firm (1987) which, along with the Pasteur Institute, has gathered many facts, presence of antibodies to only one of the glycoproteins is sufficient. Even greater difficulties arise when there are bands to gag and pol antigens in the absence of antigens to env proteins. The fact that antibodies to p24, p55, p18 and pol proteins may be encountered as well in individuals who are not infected with HIV prompted the WHO to interpret such instances as uncertain or doubtful [15].

On the other hand, some authors tend to believe that presence of more than 2 - 3 bands in any zones is a positive result [3, 8]. Moreover, there have been some

isolated reports of presence of HIV infection confirmed by detection of HIV or its antigen, with negative IEA and immune blot results [11].

Apparently, many factors, including purely technical ones, could affect immune blot results. For example, according to V. E. Berezin et al. [2], the incidence of demonstration of antibodies to different HIV proteins varied considerably, depending on the quality of antigen used.

Other technical factors may also be involved (quality of electrophoresis and electron transfer, proper identification of HIV antigen bands on a nitrocellulose replica, etc.). In spite of the fact that use of polyacrylamide gel (PAG) in a constant concentration for electrophoresis permits satisfactory separation of proteins, and in a number of instances wide bands appear on the nitrocellulose replica, which have vague margins (particularly in the range of antigens with mol. wt. of 40,000-60,000), which makes identification difficult.

In order to improve separation of HIV proteins and the quality of replicas, bearing in mind existing data [4], we used gradient PAG instead of gel in a constant concentration for the immune blot assay. We shall sum up here the data obtained with use of this modification of the immune blot test for diagnostic investigation and examination of serum from individuals infected or suspected of infection by HIV.

Material and methods. HIV producing cells (strain HTA-4) were cultured on RPMI-1640 medium with 15 percent bovine embryo serum [9]. The virus was purified by ultracentrifuging in a saccharose density gradient [12].

Electrophoresis was carried out in 4 - 20 percent PAG, pH 7.8, containing SDS, in a plate 0.85 mm thick, 160 x 160 mm in size. We used 3.5 percent concentrating gel, pH 6.8, also containing SDS. Specimens containing the virus were heated for 10 min in a boiling water bath, in lytic solution (62.5 mM tris-HCl buffer, pH 6.8; 10 percent glycerin, 2 percent SDS; 5 percent β-mercaptoethanol, 0.12 percent bromophenol blue). The electrode buffer consisted of 41 mM tris, 192 mM glycine, 1 percent SDS, pH 8.3. Electron transfer was carried out using the BioRad Trans-Blot Cell instrument at 100 V for 120 min in 25 mM tris—192 mM glycine buffer containing 20 percent ethanol. We used BioRad or LKB nitrocellulose. After electron transfer, its quality was monitored by staining membranes with 0.5 percent Ponceau solution in 5 percent trichloroacetic acid. Staining was continued for 5 min, and surplus stain was washed off in water. Then we incubated the nitrocellulose membrane in 5 percent nonfat milk (Blotto) with 0.01 M phosphate buffer, pH 7.2, containing 0.5 M NaCl in order to inactivate remaining free binding centers.

Immunoenzymatic localization of sites of HIV antigens on the nitrocellulose replica was carried out by the standard method [1].

A conjugate of IgG antibodies to the human immunoglobulin fraction with peroxidase (BioRad) was used. We used 4-chloronaphthol (Sigma).

Sera known to contain HIV antibodies, which were obtained from different places (Institute of Biomedical Research, Republic of Zaire; Johns Hopkins School of Hygiene and Public Health, Baltimore, USA; Republic Hospital in Elista, Kalmyk ASSR), as well as serum from donors and individuals in risk groups, IEA testing on whom yielded positive results twice, were submitted to the immune blot assay. In the case of vague immune blot results, the sera were submitted to the indirect immunofluorescence test using smears prepared in advance of HIV-infected cells and antihuman IgG conjugate (ICN Immunobiologicals Firm).

Results and Discussion. These studies confirmed the expediency of using gradient gel for electrophoresis and immune blot assays. The separation of HIV proteins thus obtained yields replicas of a high quality which, in turn, facilitates band identification. Analysis of the data characterizing incidence of detection of antibodies to the different HIV proteins of individuals infected with HIV and AIDS victims revealed that antibodies to high-molecular HIV glycoproteins, as well as to p55, p33 and p24 proteins were demonstrated in all serum samples from this group. Antibodies to gp41 were encountered in 90 percent of the cases and to p17, in 80 percent. Antibodies to p13 were demonstrated the least often (30 percent). The frequency of detection of antibodies to different proteins which we recorded, coincides as a whole with the data obtained by V. E. Berezin et al. [2], who used the same HIV strain. However, in our studies, as in [5], antibodies to p65 were demonstrated more often (in 58 out of 60 serum samples, or 96.6 percent). On the other hand, in the course of testing the same panel of 30 serum samples on 8 different series of immunosorbent, it was shown that the incidence of antibodies to high-molecular glycoproteins ranged from 15 to 100 percent, and it was a function of levels of these proteins in the antigens used.

This fact seems all the more important to us since it pertains to antigens, demonstration of antibodies to which is of deciding importance in verifying the diagnosis. There were three false-positive serum specimens out of the 180 submitted to immune blot assay. All these samples contained antibodies that reacted with p24 and p55 antibodies, while one of them also yielded a band situated below p65 antigen.

The table lists the results of titration of these serum samples using the immune blot, as compared to positive sera. In addition to the fact that the titers of antibodies that reacted with p24 and p55 proteins were lower, when rechecked 1 - 3 months later, they were negative in both the IEA and immune blot test. Very similar findings were made on vast material [6, 7].

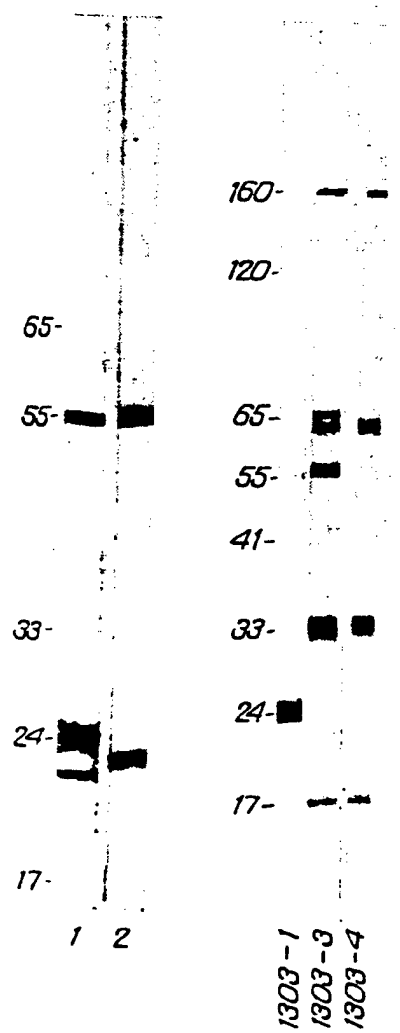
Titration of antibodies to p24 and p55 antigens in positive and false-positive serum specimens

Serum	Code	Antigen	Immune blot test results with serum in dilution of			
			1:100	1:250	1:500	1:1000
Positive	1	p24	+	+	+	-
		p55	+	+	+	-
	2	p24	+	+	+	+
		p55	+	+	+	-
	3	p24	+	+	+	+
		p55	+	+	+	+
False-positive	1	p24	+	+	-	-
		p55	+	+	-	-
	2	p24	+	-	-	-
		p55	+	-	-	-
	3	p24	+	+	-	-
		p55	+	-	-	-

At the same time, presence of antibodies in serum that interact with p24 and p55 antigens does not necessarily preclude the diagnosis of HIV infection. The following case can serve as an example. When blood was first drawn from an individual infected with HIV, serum revealed antibodies only to p24 and p55 proteins. Retesting a year later, when the subject already presented with signs of illness, revealed antibodies to env and pol antigens with some decline of antibodies to p24 protein. Testing after another six months confirmed the tendency toward decline of titer of antibodies to gag-proteins which, apparently was attributable to progression of the disease (see Figure). Essentially analogous cases are cited by F. Mozzi et al. [14].

Thus, these studies revealed that there are several factors, the most important of which is antigen quality, that are of substantial importance to effective use of immune blot assays. The antigen must contain sufficient amounts of all necessary viral proteins and, first of all, glycoproteins, which are of chief importance to formulation of a diagnosis. In spite of the fact that our studies did not include a comparative evaluation of efficacy of the standard variant of electrophoresis and electrophoresis in a PAG gradient, experience with the latter enables us to recommend it for practical use.

Our studies also indicate that detection with the immune blot test of antibodies to p24 and p55 proteins (in the absence of antibodies to glycoproteins) should not always be evaluated as a false-positive result. In such cases, blood serum must be retested.



Dynamic testing using immune blot assay of serum from HIV-infected patient

Key: 1303-1, 1303-3, 1303-4, successive sampling of serum from HIV-infected patient; 1, 2—control sera

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Prospects of the Use of Bioluminescence Methods in Medicine

917C0189 Moscow VESTNIK AKADEMII MEDITSINSKIKH NAUK SSSR in Russian No 9, Sep 90 (manuscript received 7 Feb 89) pp 31-35

[Article by I. I. Gitelzon and T. P. Sandalova, Institute of Biophysics, Siberian Branch, USSR Academy of Sciences, Krasnoyarsk]

UDC 616-073.537

[Text] The phenomenon of bioluminescence—the glowing of living organisms (bacteria, fireflies, worms, coelenterates)—is being used on an ever wider basis for practical purposes, because it enables the creation of ultrasensitive, specific methods of analysis of many biologically active substances.

By its nature, the glowing of living organisms is chemiluminescence, which is distinguished by the necessary participation of an enzyme in the reaction. The enzymes that catalyze reactions in which the energy of chemical bonds is transformed into visible light bear the general name of luciferases, although representatives of the protein family of luciferases, isolated from the organisms of various species, differ in structure and biochemical mechanisms.[4] The nature of substrates of bioluminescent reactions (their general name is luciferins) also varies—for fireflies, the luciferin is 6-hydroxybenzothiazol; for luminescent bacteria, a long-chain aliphatical-dehyde; for worms, 3-isovalerylaminopropanal; for coelenterates, coelenterazine [tselenterazin], etc.[4]

The properties of certain luciferases have been studied rather extensively. We know the amino acid sequence and the subunit composition of luciferases isolated from three species of luminescent bacterium[25-28] and three species of firefly[37,39,40] and medusa.[38] No common features have been found in the primary or quaternary structure of luciferases isolated from the organisms of different taxonomic groups. Unfortunately, no one has been able to obtain crystals suitable for x-ray analysis from any luciferase, which is why the spatial structure of those enzymes remains unknown.

The general diagram of bioluminescent reactions looks like this:

$$\text{luciferin} + O_2 \xrightarrow{\text{luciferase}} \text{oxyluciferin} + \text{light quantum}$$

Since the number of light quanta is proportional to the quantity of reacted substrate molecules, it is easily determined by measuring one parameter—the intensity of the glow. The quantum output of bioluminescence is high by comparison with that of ordinary chemiluminescent reactions. On the other hand, today's instruments for recording the amount of light have nearly reached the theoretical limit of sensitivity, which is why the sensitivity of bioluminescent methods of analysis is very high. For example, for ATP and NADPH, the sensitivity achieved in ordinary experiments is 10^{-17} - 10^{-18} M, whereas the maximum is 10^{-19} - 10^{-21}, which corresponds to 10^2 - 10^6 molecules.[36]

The most developed of the methods are those that are based on the use of luminescent systems isolated from fireflies[15,35] and luminescent bacteria.[7,14]

From a practical standpoint, the most important property of the luminescent reaction of fireflies is its requirement of ATP.[32] That enables the creation of a specific, highly sensitive rapid-analysis method for detecting that compound,[36] which makes it possible to determine the amount of ATP in a single erythrocyte and even to ascertain the difference in ATP content between erythrocytes from the same blood.[21] In determining the level of ATP, one can check for the presence of microbial infection during the production of food, pharmaceutical, and cosmetic products and in the diagnosis of bacteriuria, as well as do things such as keep track of rate of fermentation in the food and pharmaceutical industries and processes associated with waste water treatment.[15]

The use of that method for determining ATP-dependent enzymes expands considerably the possibilities associated with the use of firefly luciferase. Similar procedures have been developed for enzymes such as ATP-sulfhydrolase, hexokinase, and pyruvate kinase.[7,15,30] From the standpoint of clinical diagnostics, the most interesting is the determination of isoenzymes of creatine phosphokinase, which enables early differential diagnosis of myocardial infarction and angina pectoris.[31]

Bacterial luciferases catalyze a reaction that has a completely different biochemical basis (Fig. 1). Luminescent bacteria can be cultivated under laboratory or industrial conditions, which thereby creates an unlimited supply of reagents for bioluminescent analysis. In operation at our institute, in particular, is a semiindustrial unit that enables the production of thousands of sets of reagents for bioluminescent analysis.[16] A bioluminometer developed at our institute in conjunction with the Nauka Special Design & Technology Bureau [SKTB] (Krasnoyarsk) makes it possible to use those reagents and to create a relatively inexpensive, multifunctional system of bioluminescent analysis for clinical-diagnostic laboratories (Fig. 2).

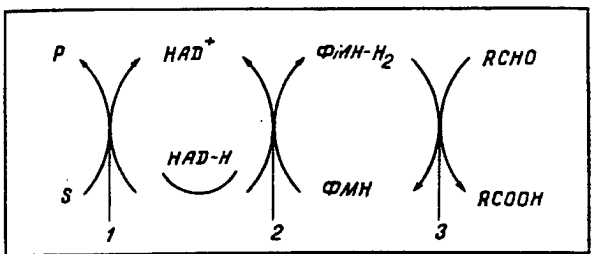

Figure 1. General diagram of reactions in which bacterial luciferase participates.

Key: 1—dehydrogenase; 2—NAD-H-FMN-oxidoreductase; 3—luciferase

Figure 2. BLM-8701 bioluminometer

From Figure 1, it follows that, with the aid of bacterial luciferase, one can record flavinmonocucleotide FMN-H_2, NAD(P)-H, long-chain aldehydes, and oxygen. However, the advantage of the bioluminescent analysis consists in the fact that, using one and the same instrument—the bioluminometer—and changing only the reagents, one can detect and measure a large quantity of biologically active substances. That is achieved by coupling the enzymes under study (their substrates or products) with luciferase (see Fig. 1). For example, the two-enzyme HAD-H system—FMN-oxidoreductase + luciferase of luminescent bacteria—is widely used for determining microquantities of NAD-H-dependent dehydrogenases.[12] The conditions for the reaction—the lack of NAD-H, the excess of dehydrogenase substrate, the low reductase content—enable the determination of the quantity of dehydrogenase from the drop in the level of luminescence. The sensitivity of the method to lactate dehydrogenase and to alcohol dehydrogenase is 0.2 mE and 1 mE, respectively, which is 20-fold higher than the sensitivity of the spectrophotometric method for measuring dehydrogenase activity. That represents a considerable advantage for the bioluminescent method, since it makes it possible to abandon the practice of drawing blood from a vein for biochemical analysis, which is quite essential in pediatrics.

As is known, the levels of lactate dehydrogenase, alcohol dehydrogenase, and aldehyde dehydrogenase in the blood serum change with various diseases, which can be used in making a diagnosis. For example, the activity of lactate dehydrogenase in acute pneumonia exceeds the level of activity of that enzyme in healthy individuals threefold or more; in individuals with mechanical jaundice, the activity of the dehydrogenases in all the samples studied was 1.5- to 2-fold higher than in healthy individuals, etc. Currently under development are methods of diagnosis based on a bioluminescent technique for determining those enzymes.

Thus, two-enzyme systems enable one to register NAD-H-dependent dehydrogenases. By using longer conjugation chains, one can measure the content of enzymes bound with dehydrogenases or the content of their substrates: ethanol and alcohol dehydrogenase, glucose and hexokinase, glucoso-6-phosphate and glucoso-6-phosphate dehydrogenase,etc.[7,15,30]

Another means of expanding the possibilities of bioluminescent methods is the use of inhibitor analysis. Bacterial bioluminescence is inhibited by a large number of xenobiotics[9] and protein molecules. Inhibitor analysis cannot always achieve the specificity in the determination of a given substance as can the use of conjugated enzyme chains, but it does enable the rapid identification of the overall toxicity of a sample.[6]

One of the modifications that was developed with the research associates of our institute makes it possible to detemine the proteolytic and antiproteolytic activity of blood plasma.[5] Figure 3 illustrates the dynamics of the activity of antiproteases in acute, uncomplicated pancreatitis and in its complications, when the activity of blood plasma inhibitors is considerably higher. Determination of antiprotease activity is a highly informative method in various diseases that occur with phenomena of endotoxicosis. A relationship has been established between signs of

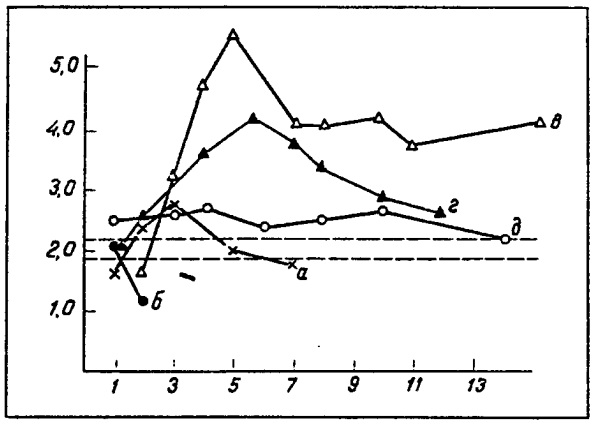

Figure 3. Dynamics of the activity of blood plasma antiproteases in pancreatitis

Key: Curve with x's represents uncomplicated pancreatitis; with solid circles, total hemorrhagic pancreatonecrosis complicated by enzymatic peritonitis and pancreatogenic shock; with open triangles, acute fatty pancreatonecrosis complicated by phlegmon of the retroperitoneal space, gland sequestration, and diffuse enzymatic peritonitis; with solid triangles, acute pancreatitis complicated by phenomena of parapancreatitis without abscess formation; with open circles, chronic pancreatitis in the stage of exacerbation; *x*-axis, observation time (in days); *y*-axis, antiprotease activity (in mg/ml) (The figure was kindly made available by S. A. Rykov)

intoxication and the level of activity of inhibitors in conditions such as acute pneumonia and purulent infection. Protease analysis takes two minutes, and 1 - 2 µl of plasma is sufficient for the testing. In light of the method's speed, it can be used for adjustment of inhibitor therapy, which is done often in acute pancreatitis, various kinds of shock, and other conditions.

A similar method was used by the research associates of our institute and the Krasnoyarsk Medical Institute for determining the seriousness of the condition of individuals with pronounced endogenic intoxication.[2] The method consists in a comparative study of the effect on the bioluminescence of the plasma of blood donors and individuals with the intoxication. The degree of severity of the illness is determined quantitatively, which is convenient in clinical practice. The method was used for predicting the course of the illness and for evaluating the effectiveness of intrasurgical sanitation of the abdominal cavity or lymph drainage. The analysis takes one minute and requires 5 - 10 µl serum.

Yet another variation of inhibitor analysis has been used for rapid determination (3-5 min) of the degree of granular damage by microscopic fungi that form aflatoxins, whose poisoning causes agranulcytosis.[29] With its high sensitivity, speed, and simplicity, the method enables one to obtain quantitative estimates of toxicity. A similar method has been used for checking the cleanliness of the skin of individuals whose work brings them in contact with platinum compounds,[8] for determining levels of phenols, quinones, organic dyes, nitrocompounds, etc.,[29] and for checking water quality.

The examples we have enumerated do not cover all the areas of use of luciferases. Recently, we have seen the publication of a good many papers devoted to enzyme immunoassay of substances, in which luciferase or its substrates have been used as the marker.[33,41] Unfortunately, the direct attachment of luciferase to an antigen or antibody results in its inactivation, which is why systems of greater complexity are used in which the formation of the antigen-antibody complex ultimately leads to the freeing of the luciferase, which lights up.

In a number of cases, methods that use not the purified luciferase isolated from luminescent bacteria, but the bacteria themselves, are informative. For example, grand prospects are attached to the determination of the activity of antibiotics in various multicomponent solutions—including biological fluids[10]; the methods take from five minutes to two hours. Used in the process are lyophilically dried cultures of bacteria that, 2-4 hours after resuspension in an appropriate medium, yield such a high level of bioluminescence that it can be seen in a dark room and, consequently, is easy to measure.

If specially selected or designed strains are used as the test subject, the number of antibiotics whose activity can be determined expands considerably.[10] The method can be used in the pharmaceutical industry for online monitoring of the accumulation of antibiotic activity in fermentation and for determining the quantity of antibiotic in the environment. Its use extends to medicine—for determining the level of antibiotics in the blood, lymph, bile, and urine—and to the food industry—for determining the level of antibiotics in food products, etc.

The luminescent bacteria DNA fragments that are responsible for the luminescence have been built into plasmids and cloned.[18] The *E. coli* bacteria that contain those plasmids synthesize luciferase in large quantities and are beginning to emit light. The use of recombinant strains containing plasmids with genes of a luminescent system has made it possible to create special indicators for individual amino acids with a sensitivity of 0.1 µg/ml and for vitamin B_{12} with a sensitivity of 0.1 ng/ml. Mutants and special recombinant strains are used for determining the mutagenic action of chemical compounds.[17]

Recently, in addition to the bioluminescent systems of bacteria and fireflies, Ca^{2+}-activated photoproteins of luminescing marine coelenterate organisms have been used. Most often, ecvorin, which is obtained from Aeguorea hydromedusas,[19] and obelin, which is isolated from Obelia hydroid polyps.[23] Photoproteins emit light only in the presence of calcium ions. That property is used for determining intracellular calcium. Those photoproteins are absolutely specific for calcium ions and are not toxic, unlike synthetic fluorescent indicators that chelate cytoplasmic calcium.[11]

Increased luminescence associated with the contraction of muscle fibers into which ecvorin was injected was first recorded by E. Ridgeway and C. Ashley,[34] and since then Ca^{2+}-activated photoproteins have become reliable, widely used bioluminescent indicators in the study of processes associated with calcium metabolism in physiological research.[19,20,22,24]

However, virtually no work has been done in the USSR involving the use of ecvorin or obelin as a Ca^{2+} indicator. That is primarily due to the high commercial price of ecvorin, which is supplied by the firm Sigma. At the moment, our institute, together with the USSR Academy of Sciences Zoological Institute, has developed a method[3] and set up production of obelin from the Obelia longissima hydroid polyp. The reagent is suitable for measuring intracellular calcium with a sensitivity of up to 10 nM.

In conclusion, we must pause to say something about the chemiluminescence of cells that is induced by the recombination of radicals and peroxides. The level of luminescence can serve as a measure of the activity of the cells releasing those substances. In particular, with specific activation of white blood cells, the process attending the formation of active forms of oxygen and, consequently, luminescence is amplified considerably. Our institute has created an automated luminometer for studying the chemiluminescence of biological objects.[13] The unit is suitable for studying any luminescent reaction; the measurement of the reaction's kinetic characteristics is done

automatically. The use of a microcomputer has provided flexibility in the choice of modes of operation and data processing.

That chemiluminometer has been used to study the specificity of the chemiluminescent response of bone marrow cells to exposure to immune serum containing antibodies against antigens—cell markers—of precursors of T-lymphocytes.[13] The participation of activated forms of oxygen in early events of cell interaction in syngenic and allogenic systems in a nonserum medium has also been demonstrated. Their detection can serve as an analytical instrument for clinical-laboratory diagnostics of immunopathology.

Thus, the principal merits of bioluminescent analysis are simplicity, high sensitivity, and speed, as well as its capability of monitoring a large number of enzymes, substrates, and substances manifesting positive or negative biological activity.

Especially important is the prospect of widespread use of bioluminescent analysis in rank-and-file clinical-diagnostic laboratories of our country, since it could in many ways compete with spectrophotometric and isotope methods of biochemical analysis. Supplying reagents and instruments on a scale that meets the needs of the country is entirely feasible. At present, the matter consists in determining the extent of the needs of the laboratory service of the country and in officially testing and certifying methods of bioluminescent analysis for clinical laboratories.

This paper has presented the results of the use of bioluminescent analysis in the Institute of Biophysics of the Siberian Branch of the USSR Academy of Sciences and in a number of clinics. It should be emphasized that bioluminescent analysis is a rapidly developing area. One can become acquainted in more detail with the state of the art in Kratasyuk and Gitelzon[7], Gitelzon *et al.*,[14] Ugarova and Brovko,[15] and Kricka.[30] One can also examine materials from international symposia on bioluminescence and chemiluminescence, the most recent of which was the fifth, which was held in Florence in 1988; its papers are published in the Journal of Bioluminescence and Chemiluminescence, 1989, No 4.

One can become acquainted in detail with the methods of bioluminescent analysis and can order the bioluminometer and sets of reagents by contacting the Institute of Biophysics, Siberian Branch, USSR Academy of Sciences, Krasnoyarsk.

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'BIOSKRIN-C' ('SOS' Chromotest Program) Automated System Solution of Ecological Genetic Problems

917C0241B Moscow ANTIBIOTIKI I KHIMIOTERAPIYA in Russian Vol 35 No 9, Sep 90 (manuscript received 10 Apr 90) pp 30-33

[Article by S. V. Vasilyeva and K. A. Iskandarova, Chemical Physics Institute imeni N. N. Semenov, USSR Academy of Sciences, Moscow]

UDC 615.7:615.33.012/-7

[Abstract] This paper summarizes the results of a comparative investigation of the SOS-inducing and mutagenic activity of a number of ecologically hazardous chemical compounds, including polycyclic aromatic compounds of ethylene imines and hydrogen peroxide. Fourteen of the 23 aromatic compounds induced frame shift mutations in *Salmonella typhimurium* test strain TA1538, but only five of these 14 were shown to induce an SOS response. The most mutagenic compounds, such as 2,7-dinitrophenanthrenequinone and 2,4,7-trinitrophenanthrenequinone, which have a biphenyl nucleus and carbonyl and nitro groups, did not induce an SOS response. It was shown that only fluorenone derivatives, mutagens whose chemical structures permit binding with DNA and which have a coplanar biphenyl structure, have SOS-inducing activity. Ames test results showed that ethylenimine and its oligomers induce base pair substitutions, but not frame shift mutations. In addition, the absence of an ethylenimine-induced mutagenic effect on *Escherichia coli* lexA cells indicates that the mutagenic effect of this compound and its oligomers is due to errors in the inducible system of SOS reparation of DNA controlled by the $lexA^+$ allele. In conclusion, results of the comparative investigation of the SOS-inducing and mutagenic activity of chemical compounds from three different classes indicate great potential for using the automated BIOSKRIN C system in ecological investigations. Tables 2; references 16: 2 Russian, 14 Western.

Inversion Voltammetric Determination of Heavy Metal Ions in Water

917C0242A Moscow GIGIYENA I SANITARIYA in Russian No 11, Nov 90 (manuscript received 6 Jul 89) pp 93-94

[Article by A. I. Kamenev, I. P. Viter, Ye. F. Gorshkova and G. V. Guskov, Moscow State University imeni M. V. Lomonosov; Moscow Scientific Research Institute of Hygiene imeni F. F. Erisman]

UDC 614.777:546.3]-074

[Abstract] Inversion voltammetry was applied to the analysis of zinc, cadmium, lead and copper in drinking and waste waters. The optimal conditions were determined as requiring 0.01 - 0.025 M phosphoric acid, 7 x 10E-6 M mercury ions, and recording of inversion voltammetric signals at a scanning rate of 3 - 5 V/sec. The relative analytical error did not exceed 3 - 4 percent, with the technique applicable to water samples with BOD of < 20 mg/L. Figures 2; references 4: Russian.

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